Dexcom | G5® mobile

CONTINUOUS GLUCOSE MONITORING SYSTEM

Advisory Committee Briefing Materials
July 21, 2016

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Dexcom, Inc. CD

SECTION 1

Sponsor Executive Summary

DEXCOM G5 MOBILE SYTEM CONTINUOUS GLUCOSE MONITOR FOR NON-ADJUNCTIVE USE IN THE TREATMENT OF DIABETES MELLITUS

EXECUTIVE SUMMARY FOR THE CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL MEETING

MEETING DATE: 21 July 2016

PANEL MEETING BRIEFING MATERIALS:

AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

CGM	Continuous Glucose Monitor
DCCT	Diabetes Control and Complications Trial
FDA	Food and Drug Administration
HbA1c	Glycosylated Hemoglobin
IAF	Insulin Adjustment Factor
IFU	Instructions for Use
ISF	Insulin Sensitivity Factor (mg/dL/IU)
IU	Units of Rapid Acting Insulin
MARD	Mean Absolute Relative Difference
PMA	Premarket Approval Application
SMBG	Self-monitoring of Blood Glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
YSI	Yellow Springs Instruments

1 SYNOPSIS

The Dexcom G5® Mobile Continuous Glucose Monitoring System (Dexcom G5 Mobile System) is a continuous glucose monitoring (CGM) device that was approved by the Food and Drug Administration (FDA) on August 19, 2015. Previous generations of the Dexcom CGM have been approved since March 24, 2006. Currently, the Dexcom G5 Mobile System is indicated for detecting trends and tracking patterns in blood glucose in patients with diabetes as an adjunctive device to complement, but not replace, information obtained from standard home glucose monitoring devices ("adjunctive indication"). Dexcom is seeking to modify the current indication to state that the Dexcom G5 Mobile System is designed to **replace** fingerstick blood glucose testing for diabetes treatment decisions ("non-adjunctive indication"). Treatment decisions include daily choices made by people with diabetes, such as determining an insulin dose, ingesting carbohydrates, or assessing when to wait before dosing or eating.

The change to the indication will not require changes to the system components, and the system will still require calibration with a fingerstick taken by self-monitoring of blood glucose (SMBG, also known as a blood glucose meter) every 12 hours. The primary modification will be in the Instructions for Use (IFU). The instructions specifically related to making treatment decisions with CGM can be found in Section 8 of the proposed Getting Started Guide included in the briefing materials. Aside from the additional section and changes to the safety statement, this Getting Started Guide is very similar to that which has been used with the Dexcom G5 Mobile System since its approval in August 2015.

Based on discussions with the FDA during pre-submission meetings and the ten-year history of clinical studies and commercial use of Dexcom CGMs, it was determined that the indication change could be supported by computer simulations that could challenge the extremes in product use and human factors analyses to ensure safe and effective non-adjunctive use of the Dexcom G5 Mobile System. This panel pack contains an overview of two simulated studies (Section 7.3) and a Human Factors Usability Study (Section 9) to support safety and effectiveness. The simulation studies investigate the risks and benefits associated with non-adjunctive use of the Dexcom G5 Mobile System to identify specific situations, behaviors, or physiological conditions that may elevate risks or provide benefit for CGM-based treatment decisions relative to decisions made using SMBG. Two simulations were conducted: the first evaluated the safety and effectiveness of CGM relative to SMBG in patients with Type 1 Diabetes (T1D) over a two-week period; the second evaluated the risks of hypo-and hyperglycemia in T1D with meal time insulin decisions based on CGM versus SMBG. The Human Factors Usability Study evaluated the revised IFU.

1.1 OVERVIEW OF CURRENT DEXCOM G5 MOBILE SYSTEM

FDA approved the Dexcom G5 Mobile System in August 2015. This CGM system is derived from the commercialized G4 PLATINUM CGM System (G4 System), initially approved by FDA in October 2012. The Dexcom G5 Mobile System includes the same functionality as the G4 System with the addition of

wireless Bluetooth® technology to allow glucose data to be sent directly to an app on iOS-enabled devices.

In the US, the Dexcom G5 Mobile System is indicated for detecting trends and tracking patterns in patients with diabetes as an adjunctive device to complement, but not replace, information obtained from standard home glucose monitoring devices.

In the European Union, the Dexcom G5 Mobile System received CE Mark (i.e. regulatory approval) in May 2015. The CE mark version of the CGM is indicated to be used non-adjunctively for diabetes treatment decisions.

The Dexcom G5 Mobile System is designed to provide continuous measurement of glucose concentration over a 40-400 mg/dL range. The device is small and portable and displays glucose reading,[1] trends, and rates of change to patients in real-time. The system also provides alerts and alarms when glucose levels reach a high or low threshold. The Dexcom G5 Mobile System is intended for single patient use in the US and requires a prescription. The system consists of four principal components (Figure 1): a sensor, transmitter, receiver, and mobile app.

Figure 1: Dexcom G5 Mobile System

[1] "Number" is the layman's term used in the instructions to help users remember a CGM reading is required. The CGM reading is the number in units of mg/dL.

The sensor is a glucose-oxidase-based wire that continuously measures glucose in the interstitial fluid. The sensor is inserted just under the skin and held in place with medical adhesive on the skin surface. It is worn for up to seven days, when it is then disposed of and replaced with a new sensor. The transmitter is attached to the sensor and converts an electrical current produced by the sensor to glucose readings using an onboard algorithm, Software 505. The Software 505 algorithm was first approved in the G4 System and is incorporated in clinical studies under that name. The transmitter contains wireless Bluetooth® technology and sends glucose data to the receiver and/or mobile app at regular five minute intervals. The sensor and transmitter are water resistant, and the entire Dexcom G5 Mobile System is wireless.

The receiver and iOS compatible mobile app provide users with a real-time visual display of glucose readings and trend information. The receiver and mobile app also contain configurable alerts to notify patients when glucose levels reach high or low thresholds. Additionally, the receiver and mobile app have a non-configurable low blood glucose alarm at 55 mg/dL to provide patients additional warnings of hypoglycemia. This alarm cannot be changed, and it repeats every five minutes if the user does not acknowledge it, thereby providing an extra layer of protection for users who may experience symptoms of hypoglycemia unawareness or users who are sleeping or otherwise not paying attention to their glucose levels.

The Dexcom G5 Mobile System requires twice daily calibration with capillary blood glucose information from any FDA cleared commercially distributed SMBG. When a calibration is necessary, the receiver and/or mobile app prompts the user to enter a value obtained from SMBG.

Information from the Dexcom G5 Mobile System can be shared in real-time through the internet to another person's mobile device so that the second person can be made aware of the user's alerts and glucose levels. This provides another layer of protection for children and for users who may experience dangerous episodes of severe hypoglycemia where they are unable to react or care for themselves. The information can also be uploaded to the Dexcom CLARITY™ Diabetes Management Software, allowing users and healthcare professionals to view historic trends and patterns.

The system requires a prescription and is indicated for patients two years and older.

1.2 UNMET MEDICAL NEED

CGM has been shown to provide a significant benefit in diabetes treatment, including reduced excursions of hypoglycemia and hyperglycemia (Garg et al, 2006) and reduced glycosylated hemoglobin (HbA1c) (Foster et al, 2016). Therefore, there is a need to expand the use of CGM among the population of people with diabetes. However, this expansion is currently limited by the indicated requirement to confirm CGM readings with SMBG before making treatment decisions. Some users who are already using CGM trust it enough to make treatment decisions, thereby using the device off-label. Dexcom is unable to train these patients in the proper use of CGM to make treatment decisions because doing so would be promotion of unapproved uses. In order to expand CGM to a broader population and to provide appropriate training, Dexcom is seeking to revise the indications for use.

T1D and advanced Type 2 diabetes (T2D) require intensive insulin therapy in combination with frequent blood glucose monitoring to optimize glycemic control. Without this control, the effects of chronic hyperglycemia may include nephropathy, retinopathy, neuropathy, and cardiovascular disease (The Diabetes Control and Complications Trial Research Group, 1993). Because insulin has a narrow therapeutic window, hypoglycemia is an inevitable consequence of intensive insulin use due to imbalances between insulin dose, activity, and carbohydrates ingested (Smart et al., 2012; Virdi et al, 2012). Therefore, attempting to reduce chronic hyperglycemia may cause hypoglycemia, a more imminent risk.

Episodes of hypoglycemia can have deleterious consequences ranging from interruption of normal activities to loss of consciousness, seizures, and even death (International Hypoglycaemia Study Group, 2015). Intensive diabetes management has been associated with an increased frequency of severe hypoglycemia; one particular area of concern is in children at night. In cases of nocturnal hypoglycemic seizure in children, a glucose level of less than 60 mg/dL was documented 2.25-4 hours before the seizure (Buckingham et al, 2008). As a result of this increased frequency of hypoglycemia, many patients and caregivers reduce insulin doses, leading to chronic hyperglycemia (Andebro et al, 2010; International Hypoglycaemia Study Group, 2015). Detection and prevention of both hypoglycemia and hyperglycemia are critical for optimal glycemic control and cannot be obtained even with frequent self-monitoring (American Diabetes Association, 2015).

Despite the awareness of these challenges and advances in diabetes treatment, less than 30% of people with T1D have acceptable glycemic control, defined as HbA1c < 7.0% or lower for adults and 7.5% or lower for children under the age of 19 (Handelsman et al, 2015; Miller et al, 2015). One of the primary reasons for this lack of glycemic control is that the majority of patients do not monitor their blood glucose frequently enough. For most patients on intensive insulin treatment, the American Diabetes Association recommends SMBG six to ten (or more) times daily (American Diabetes Association, 2016). However, the majority of patients do not comply with this recommendation; only 20% of patients with T1D test seven or more times per day (Miller et al, 2015).

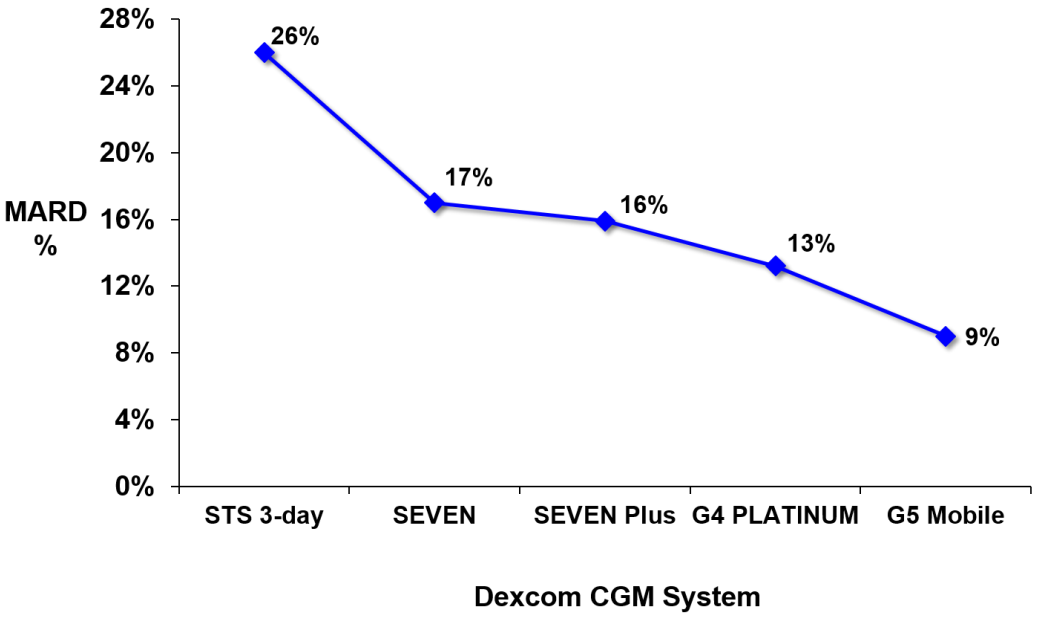
Patients with T1D do not comply with the recommendation for a variety of reasons. Frequent SMBG presents a burden to patients, including pain and discomfort, the need to have clean hands,[2] the need to carry equipment, the embarrassment of highlighting one's disease in public, and the perceived limited utility of SMBG results (Fisher et al, 2011). The limited utility may be due in part to the fact that data provided by SMBG is also limited; glucose meters merely measure the glucose value at a point in time and do not offer any information about blood glucose direction or rate of change. Further, many SMBG devices do not meet the current ISO standards for accuracy (Freckmann et al, 2012; Hasslacher et al, 2014), and some patients do not use appropriate SMBG techniques when required to perform numerous fingersticks a day. The lack of blood glucose testing is of particular concern for the approximately 20% of

[2] The need for clean hands is especially noteworthy in pediatrics.

patients who have impaired hypoglycemia awareness (i.e., do not experience or notice hypoglycemia symptoms until their blood glucose is extremely low) (Graveling and Frier, 2010).

People with diabetes experience frequent changes in glucose levels throughout the day due to meals, activity, stress and illness. CGM captures these normal daily excursions. Since the first approval and commercial launch of Dexcom CGM devices in 2006, the point accuracy of Dexcom CGM has continuously improved. Figure 2 shows the evolution of the mean absolute relative difference (MARD) of Dexcom CGM readings compared to reference values obtained from plasma glucose measurements using from a lab analyzer, Yellow Springs Instrument (YSI). The MARD indicates the average difference or distance between the CGM and YSI values. Lower MARD indicates better accuracy. The current Dexcom G5 Mobile System point accuracy is a MARD of 9%. The Dexcom G5 Mobile's algorithm helps identify and discard outlier calibrations, and it is complemented by enhanced decision support from CGM trend information (direction of change) and alerts. In contrast, a patient basing decisions on an inaccurate SMBG value has no mitigations to identify or address the inaccuracy and could make a potentially harmful decision.

Figure 2: Evolution of Dexcom CGM Accuracy



It is important to reiterate that the Dexcom G5 Mobile System provides information on the rate and direction of glucose change. This additional awareness allows people with diabetes to make more informed treatment decisions rather than basing those decisions on a static point glucose reading. This awareness also allows users to associate changes in glucose values to their personal activities (e.g., eating, exercise). Consider the scenario below in Figure 3.

Figure 3: Example of Uncertainty in Diabetes Management Decisions Based On Episodic SMBG

Assume a person using intensive insulin measures their glucose 2-3 hours after a meal dose and a meal, before driving or going to sleep, and the glucose is accurately measured at 102 mg/dL. • **Should a snack be recommended?** • **Would the decision change if there was knowledge about whether glucose is rising or falling?** • **Would the presence of hypo or hyperglycemia alert change the recommendations?**		

CGM has been shown to reduce both hypoglycemic and hyperglycemic excursions compared to SMBG, even in early generations of CGM (Garg et al, 2006). The authors suggested that this reduction in hyperglycemia without increasing the risk of hypoglycemia may reduce long-term diabetes complications. Additional studies show that CGM users have lower HbA1c (Foster et al, 2016), which may be due to the fact that CGM offers crucial tools for diabetes management:

- Configurable alerts for passing user-specified high and low glucose levels
- Configurable alerts for increases in speed of glucose level
- Fixed alarm for low glucose levels that repeats until acknowledged and cannot be disabled
- Continuous glucose trend display showing glucose levels throughout the day
- Arrows highlighting the speed and direction of glucose level changes
- Event markers to track activities, meals, insulin doses, and illness to help correlate events with glucose levels
- Algorithm to identify outlier (“bad”) calibrations and potentially inaccurate (“noisy”) sensors

The alerts and alarm inform patients of dangerous changes that they might not otherwise notice, such as in cases of severe nocturnal hypoglycemia. In cases such as these, CGM helps to prevent episodes of hyper- and hypoglycemia by increasing awareness of glucose levels. CGM has a profound impact on diabetes management by improving detection and prevention of hypoglycemic events, minimizing hyperglycemic excursion, and providing immediate feedback on the therapeutic decisions that people with diabetes make multiple times per day.

There is a significant need to expand the use of CGM to improve glycemic control in patients with T1D and T2D with intensive insulin treatment. Despite the benefits of CGM, it is currently only used by approximately 16% of patients in the T1D exchange, a large registry of over 80 clinical practices from leading diabetes centers across the United States. A substantial barrier to CGM use for patients, prescribers, and payers is the ongoing need for SMBG while using a CGM device. However, if CGM provided an alternative to SMBG rather than an addition to SMBG, users will likely be more willing to adopt this technology and benefit from the continuous information and alerts. In addition, with fewer

SMBG fingersticks required a day, users may be more careful and precise with the fingersticks they do perform.

Even with the current adjunctive indication, many patients are already using CGM non-adjunctively to make treatment decisions. A review of recent studies indicates that patients perform less frequent SMBG after initiating CGM use (Battelino et al, 2012; Bergenstal et al, 2013; Chamberlain, et al., 2015; DirecNet Study Group, 2008; New et al, 2015; Riveline et al, 2012; Wong et al, 2014). Recent data show that this reduction in SMBG does not result in increased HbA1c (ADA Symposium, June 2016, results pending publication).

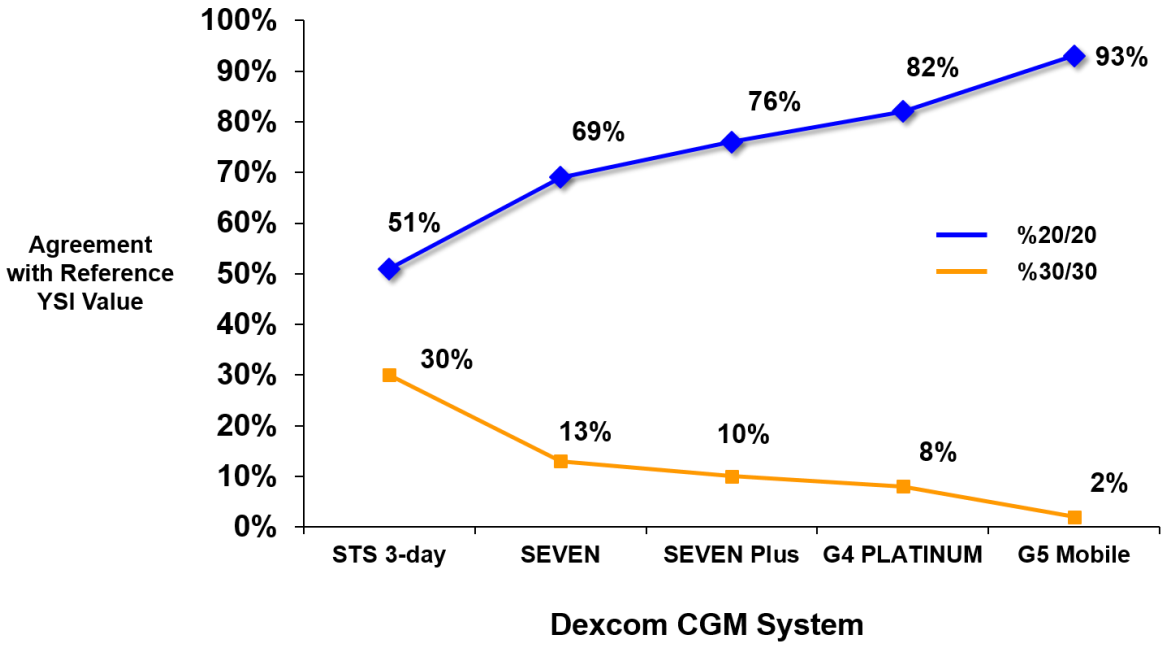
In the current training materials, there are no instructions for patients regarding when to use their CGM to make treatment decisions, and more importantly, when not to use their CGM to make treatment decisions. Non-adjunctive labeling would allow Dexcom to educate patients and clinicians about appropriate CGM use for treatment decisions, including the key information required for making CGM-based treatment decisions (CGM reading and arrow) and situations when users should not treat based on CGM (no CGM reading, no arrow, acetaminophen ingestion).

1.3 CLINICAL STUDIES

The commercially available Dexcom G5 Mobile System is Dexcom's most accurate CGM system to date and is the first continuous glucose sensor to be considered by the FDA for non-adjunctive use. CGM accuracy is measured by the MARD from a patient's reference values obtained from blood glucose measurements from a lab analyzer, YSI. YSI measures glucose concentration in plasma samples obtained from venous blood draws while the CGM sensor measures glucose in the interstitial fluid. The MARD indicates the average difference or distance between the CGM and YSI values by comparing the YSI blood glucose value to a CGM glucose reading taken immediately after the YSI was collected. The MARD of Dexcom CGMs has steadily decreased from 26% with the first generation STS device in 2006 to 9% in adults (10% in pediatrics) for the Dexcom G5 Mobile System with Software 505 (Figure 2) in 2015.

Since CGM values that are grossly increased or decreased relative to a reference value would increase risk to a patient using this information to dose insulin, the extent of highly erroneous, or outlying, CGM values is extremely important. A non-adjunctive CGM device would thus need to have an extremely high percentage of point values close to the reference value (within 20%) and an extremely small number of outlier values (>30% compared to a reference YSI value) to ensure that an accurate CGM value was being used for a diabetes treatment decision. The continuous improvement in reducing these outlier values in Dexcom's CGMs is illustrated graphically in Figure 4 for adults.

Figure 4: Improved Agreement of CGM Values to YSI Values for Adults



This FDA-approved Dexcom G5 Mobile System is the result of over ten years of research and development by Dexcom in CGM technology. Improved accuracy has been achieved through advancements in sensor technology, manufacturing and signal/calibration algorithm management.

A large body of clinical evidence has demonstrated the safety and effectiveness of Dexcom CGMs over the last decade. These studies were submitted to the FDA and provided the foundation for regulatory approval of the CGM systems. Summary results from key clinical studies, shown in Table 1, illustrate the improved performance of Dexcom CGMs. A description of each study is provided in Section 7.1.

Table 1: Summary of Key Dexcom Clinical Studies

Dexcom CGM (population studied)	Year	Total # of Subjects	Matched CGM to YSI Pairs	Mean Absolute Relative Difference	% 20/20[1]	>%30/30[2]
STS 3 day (adults)	2005	91	653	26.2%	50.5%	30.2%
SEVEN (adults)	2006	72	1638	16.6%	69.1%	12.8%
SEVEN Plus (adults)	2008	53	1827	15.9%	76.1%	9.6%
G4 PLATINUM (adults)	2012	72	9093	13.2%	81.7%	7.8%
G4 PLATINUM (pediatrics)	2012	176	2922	17.4%	68.1%	15.4%
G4 PLATINUM with Software 505 (adults)	2014	51	2263	9.0%	93.0%	2.0%
G4 PLATINUM with Software 505 (pediatrics)	2014	79	2262	10.4%	90.6%	3.8%

1 The percentage of CGM values that are within ±20 mg/dL of the paired YSI value at reference levels ≤80 mg/dL or within ±20% at reference levels >80 mg/dL
2 The percentage of CGM values that are greater than ±30 mg/dL of the paired YSI value at reference levels ≤80 mg/dL or greater than ±30% at reference levels >80 mg/dL

No additional clinical studies were performed in support of the proposed non-adjunctive indication. However, clinical performance of Dexcom CGM with the Software 505 algorithm, which is used in the Dexcom G5 Mobile System, was evaluated in two separate clinical studies, one with adults and one with pediatrics. A subset of the clinical data used to obtain FDA approval of the Software 505 algorithm is included in Section 7.1.1. Additional information is also provided in the briefing materials.

After discussions with FDA, it was determined that it was difficult to appropriately size a premarket clinical study to capture the potential new risks associated with the indication change, given that these risks (such as severe hypoglycemia) are rare in the confines of a clinical trial and occur at a low frequency in the normal diabetic population. The Dexcom G5 Mobile System is commercially available, and the safety and effectiveness of current use has been established through clinical studies and post-market surveillance. FDA indicated that the Dexcom G5 Mobile System may have adequate accuracy, as demonstrated by the adjunctive clinical studies, to be used in a non-adjunctive setting, if the benefits should outweigh the risks of such an indication. Thus, it was mutually decided to focus on simulation

testing to assess potential risks. In a simulation, hypoglycemia can be modeled directly, without exposing patients to any risks of these events. The simulation data, described in the section below, provides reasonable assurance of safety and effectiveness for non-adjunctive use of the Dexcom G5 Mobile System.

1.4 SIMULATION STUDIES

In January 2014 FDA produced a draft guidance titled "Reporting of Computational Modeling Studies in Medical Device Submissions." In parallel, FDA contributed to the establishment of an ASME Standardization Committee V&V-40 "Verification and validation in computational modeling of medical devices."

In Silico Clinical Trials (ISCT) are defined as "the use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention" (Viceconti et al, 2016). These simulations recreate the concept of an *in vivo* trial using an *in silico* approach, where a large number of individual patients is modeled by initializing a disease/intervention model with quantitative information either measured on an individual (subject-specific model) or inferred from population distributions of those values (population-specific model).

An essential requirement to perform large scale ISCT is the availability of an individualized model of a patient's physiological response to the drug- or medical device-based treatment under test that accounts for inter-individual variability and is able to describe a large number of individual virtual subjects (VS).

Dexcom performed two distinct simulations:

- **Two-week Simulation Study.** The first simulation was a two-week simulated clinical study (an ISCT) that compared glycemic outcomes (time in range, time in hyperglycemia, time in hypoglycemia, and average rate and average duration of hypoglycemic events) from CGM and SMBG-based treatment decisions. This simulation was intended to assess the **overall** risk of CGM-based dosing decisions compared to SMBG, following 200 simulated virtual T1D patients (100 adults; 100 pediatric) over the course of a two-week period. This simulation was conducted in collaboration with the University of Padova. Patient behavioral assumptions were intended to reflect real-life patients and assumptions were derived from the literature, Dexcom clinical studies and field data, and common clinical practice. The ISCT allowed a direct comparison of the benefit-risk profile of CGM-based decision making versus SMBG-based decision making over multiple meals over multiple days in a large number of virtual subjects with diverse behaviors.
- **Meal Dosing Simulation.** Dexcom conducted a second simulation to assess **individual** risks associated with CGM and user behavior, compared to SMBG. This simulation used a simplistic model for single meal-time dosing and was intended to identify specific situations that could result in high risk (hypoglycemia and hyperglycemia) with non-adjunctive CGM use. The model was designed to represent a single decision (not two-weeks of wear) made by CGM versus one

made by SMBG. Both the SMBG-based and CGM-based insulin doses were determined using the standard bolus equation; however, the CGM-based dose was adjusted up or down based on rising or falling glucose (i.e., trends and trend arrows). That single decision was repeated with various parameters to determine if they led to different results. This simulation model allowed for individual manipulation of physiological and situational parameters providing a rapid evaluation of the impact of each parameter on risk of hypoglycemia and hyperglycemia.

The combination of both the two-week simulation and meal-time dosing simulation provide a direct comparison between CGM and SMBG when used for diabetes decision-making and also identified specific situations that elevated risk for CGM-based treatment decisions

1.4.1 TWO-WEEK SIMULATION STUDY

1.4.1.1 Background and Methods

The two-week non-adjunctive use simulation study (two-week simulation study) evaluated safety and effectiveness of non-adjunctive use of the Dexcom G5 Mobile System compared to SMBG using a T1 Diabetes Decision Making Model. An overview of this simulation study is provided in Table 2.

Table 2: Overview of 2 Week Non-adjunctive Use Simulation Study

Study Duration	14 days (2 seven day CGM sessions)
Population	200 total (100 adult virtual subjects and 100 pediatric virtual subjects)
Behaviors	100 different randomizations of behavioral parameters were modeled for each virtual subject
Hypoawareness Groups	2 groups were simulated 1. Mixed hypoawareness: 80% normal awareness, 20% impaired awareness 2. Impaired hypoawareness: 100% impaired awareness
Outcome Metrics	1. Time in severe hypoglycemia (below 50 mg/dL) 2. Time in hypoglycemia (below 70 mg/dL) 3. Time in target glucose range (between 70 mg/dL and 180 mg/dL) 4. Time in hyperglycemia (above 180 mg/dL) 5. Average rate and average duration of events below 70 mg/dL and 50 mg/dL

The T1D Decision Making Model (T1D-DM Model) used in this simulation study consists of four main components:

1. UVA/Padova T1D Simulator

   The UVA/Padova T1D Simulator is a validated large-scale maximal computer model of glucose, insulin and glucagon dynamics in T1D patients jointly developed by the University of Virginia

(Charlottesville, Virginia) and the University of Padova (Padova, Italy). The simulator was accepted by the FDA in 2008 as a substitute to animal trials for the preclinical testing of certain insulins. This simulator has been used by 32 research groups in academia and five companies, leading to more than 63 publications in peer-reviewed journals. The simulator has been adopted by the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Consortium to test control algorithms and accelerate closed-loop studies, with a number of Investigational Device Exemption approvals achieved based upon simulation only.

The model for the UVA/Padova T1D Simulator was derived initially from 204 actual nondiabetic individuals but was modified to account for the glucose-insulin dynamics found in people with T1D. The simulator has been updated in 2013 (Dalla Man et al., 2014), including an improved model of the glucose kinetics in hypoglycemia and models of glucagon kinetics, secretion and action. The updated simulator was validated using T1D data sets (Visentin *et al.*, 2014). In 2015 (Visentin *et al.*, 2015), a circadian model of insulin sensitivity was also incorporated, thus extending its validity from simulation of a single meal to simulation of multiple days. A total of 100 virtual adult and 100 virtual pediatric subjects were created to cover the range of physiological parameters expected in the T1D population. Each virtual subject is described by a set of physiological parameters describing glucose gastro-intestinal absorption, endogenous production and utilization, insulin subcutaneous absorption, action and degradation, and glucagon secretion, action and degradation.

2. Glucose monitoring model (SMBG or CGM)

   This model simulates either SMBG measurements or CGM outputs, including CGM glucose trace, trend arrows, high/low glucose alerts and low glucose alarms, based on simulated blood and interstitial glucose provided by the simulator. In the CGM model, glucose readings are generated by applying error models that include the major sources of CGM inaccuracy, such as systematic biases due to imperfect calibration and measurement noise. CGM model parameters were derived from four clinical datasets (two in adults and two in pediatrics) used to approve the Software 505 algorithm.[3] SMBG errors were simulated using a model of the statistical distribution of the SMBG measurement error in the adult clinical dataset used to approve the Software 505 algorithm.

3. T1D therapy model

   The T1D therapy model simulates the patient behavior of administering insulin or consuming carbohydrates based on SMBG or CGM glucose values. The therapy model has inputs of meal

[3] The same algorithm used in the Dexcom G5 Mobile System.

information, glucose information from SMBG or CGM, and individual subject therapy parameters. It outputs the carbohydrate intake and insulin boluses. The therapy model also uses hypoglycemic symptoms to trigger treatments.

4. Insulin pump model

   The insulin pump was used as the device model for continuous-time infusion of rapid-acting insulin in the subcutaneous insulin. The total infusion was defined as the sum of the bolus infusion plus the constant basal infusion. The bolus administration was an impulsive administration of insulin as calculated by the T1D therapy model whereas the basal administration was a constant infusion rate (basal = 0.47 x total daily insulin) as determined by a guideline by Davidson et al (Endocrine Practice, 2008).

Details of the model are provided in Section 7.3.2.1.

Using the T1D decision making model, simulations were run in a total of 200 virtual subjects with unique physiologies (i.e., each virtual subject was intended to represent a different patient with T1D) over a simulated two-week period, reflecting a total of two CGM wear sessions. These subjects had a mixture of hypoglycemia awareness[4] and subject behaviors, resulting in 40,000 combinations, to comprehensively assess the risks and benefits of CGM-based decision making versus SMBG-based decision making.

Three meals per day were randomly generated for each subject. CGM high and low glucose alert thresholds were varied across subjects that were based upon actual use of the product in the real world. The Dexcom G5 Mobile System requires that the sensor be replaced after seven days of use; therefore, two sensors, each lasting seven days, were simulated per subject. Additionally, CGM sensor calibrations were assumed to occur at 6:00 AM and 6:00 PM.

Each virtual subject (with the same physiologies and behaviors) had two simulations run: one where SMBG was used for diabetes treatment decisions and one where CGM was used for diabetes treatment decisions. This allowed Dexcom to compare decisions based on CGM data with decisions based on SMBG measurements simultaneously on the same virtual patient in parallel, eliminating potential physiological differences that could occur between cohorts or behavioral changes that could occur over time in clinical studies. The virtual subject acted as his own control.

[4] A patient with hypoglycemia unawareness is at higher risk of severe hypoglycemia from insulin-dosing because characteristic symptoms of hypoglycemia (such as palpitations, sweating and anxiety) are not readily recognized at normal low glucose levels. So the simulation included two groups of hypoawareness, one of which had all subjects experiencing impaired hypoawareness. Since Olsen et al. report that about 20% of general population has impaired hypoglycemia awareness, the mixed hypoawareness group consisted of 80% of subjects with normal hypoawareness and 20% with impaired hypoawareness.

To compare the impact of CGM-based treatment decisions versus SMBG-based decisions, we assessed, for each combination of virtual subject and behavior, the following glycemic outcomes used as common endpoints in diabetes trials (Battelino et al, 2012; Juvenile Diabetes Research Foundation, 2010):

1. Time in severe hypoglycemia (below 50 mg/dL)
2. Time in hypoglycemia (below 70 mg/dL)
3. Time in target glucose range (between 70 mg/dL and 180 mg/dL)
4. Time in hyperglycemia (above 180 mg/dL)
5. Time in severe hyperglycemia (above 250 mg/dL)
6. Average rate and average duration of events below 70 mg/dL and 50 mg/dL

1.4.1.2 Results

Simulation data show that the amount of time subjects spent below 50 mg/dL was reduced for the impaired hypoawareness group for both adults and pediatrics when CGM was used for treatment decisions (Table 3). The results were similar for CGM- and SMBG-based decisions for the mixed hypoawareness group, although the CGM group had a higher percent of virtual subject behaviors with time spent below 50 mg/dL of less than 5 minutes than the SMBG group.

Table 3: Time Below 50 mg/dL Across All Days of Sensor Wear

	Mixed Hypoawareness		**Impaired Hypoawareness**	
	SMBG	**CGM**	**SMBG**	**CGM**
ADULTS				
Median (25th - 75th Percentile) minutes/day	0 (0-1.8)	0 (0-1.4)	3.9 (0-10.3)	1.4 (0-4.6)
% of Virtual Subjects with Time <5 minutes/day	88%	91%	56%	77%
PEDIATRICS				
Median (25th - 75th Percentile) minutes/day	0 (0-0)	0 (0-0.3)	1.4 (0-4.9)	0 (0-2.1)
% of Virtual Subjects with Time <5 minutes/day	95%	97%	76%	92%

Both the average event rate, which is the number of events below 50 mg/dL per virtual subject with a specific behavior per week, and the average duration of events below 50 mg/dL were reduced with CGM (Table 4).

Table 4: Average Rate and Average Duration of Events Below 50 mg/dL Across All Days of Sensor Wear

	Mixed hypoawareness		Impaired hypoawareness	
	SMBG	**CGM**	**SMBG**	**CGM**
ADULTS				
Average Rate [per VSB-week]	0.57	0.46	1.58	0.95
Average Duration [min] (±SD)	25.94 (±16.99)	21.85 (±11.50)	31.86 (±19.91)	24.64 (±12.52)
PEDIATRICS				
Average Rate [per VSB-week]	0.24	0.23	0.83	0.47
Average Duration [min] (±SD)	26.94 (±20.56)	20.03 (±11.84)	31.24 (±22.64)	22.01 (±13.01)

This simulation identified one potentially higher risk of using CGM for treatment decisions on the first day of sensor wear for pediatric subjects (but not for adult subjects). While the average rates of events below 50 mg/dL and 70 mg/dL were higher for pediatrics making CGM-based treatment decisions on Day 1, the average duration of these events was noticeably reduced with the use of CGM (Table 5). This suggests that the CGM's low glucose alert and alarm effectively mitigated this risk by decreasing the duration of events if they occurred.

Table 5: Average Rate and Average Duration of Events Below 50 mg/dL and 70 mg/dL for Pediatric Subjects on Day 1 of Sensor Wear

		Mixed hypoawareness		Impaired hypoawareness	
		SMBG	**CGM**	**SMBG**	**CGM**
Events below 50 mg/dl	Average Rate [per VSB-week]	0.29	0.46	0.88	0.89
	Average Duration [min] (±SD)	25.76 (±17.58)	21.28 (±11.45)	31.61 (±22.10)	24.41 (±13.01)
Events below 70 mg/dl	Average Rate [per VSB-week]	2.02	2.60	1.98	2.56
	Average Duration [min] (±SD)	55.58 (±36.92)	42.93 (±25.83)	91.60 (±50.58)	55.75 (±33.37)

Increasing time in the target glucose range is a goal of diabetes management. CGM-based treatment decisions resulted in slightly more time spent in the target glucose range of 70 mg/dL-180 mg/dL for both adult and pediatric subjects. This trend was seen for both hypoawareness groups. No safety risks were identified for CGM (Table 6).

Table 6: Time Spent in Target—Between 70 mg/dL and 180 mg/dL

	Mixed Hypoawareness		Impaired Hypoawareness	
Time Between 70-180 mg/dL	**SMBG**	**CGM**	**SMBG**	**CGM**
Adult Median hours/day (25th - 75th Percentile)	15.8 (13.8-18.1)	16.2 (14.4-18.3)	15.6 (13.7-17.9)	16.2 (14.5-18.3)
Pediatric Median hours/day (25th - 75th Percentile)	14.1 (12.0-16.4)	14.3 (12.3-16.5)	14.0 (11.9-16.24)	14.3 (12.2-16.5)

Reducing time spent above 250 mg/dL is important for diabetes management because hyperglycemia can adversely impact HbA1c and result in diabetic ketoacidosis if not controlled. Simulations showed that time spent above 250 mg/dL is reduced by non-adjunctive use of CGM relative to SMBG use in both adults and pediatrics (Table 7). Hypoglycemia awareness did not have an impact on this result. No risks of using CGM for treatment decisions were identified.

Table 7: Time Spent Above 250 mg/dL

	Mixed Hypoawareness		Impaired Hypoawareness	
Time >250 mg/dL	**SMBG**	**CGM**	**SMBG**	**CGM**
ADULTS				
Median minutes/day (25th - 75th Percentile)	125.6 (62.6 - 211.8)	119.1 (59.7-197.9)	125.2 (62.3-212.1)	118.2 (59.7-198.2)
% of Virtual Subjects with Time <6 hours/day	67%	70%	67%	70%
PEDIATRICS				
Median minutes/day (25th - 75th Percentile)	212.6 (116.9-330.8)	200.2 (112.4-309.6)	212.1 (116.3-329.6)	200.6 (112.71-409.3)
% of Virtual Subjects with Time <6 hours/day	43%	45%	43%	45%

Table 8 provides a summary of the outcomes of this two week simulation study. Overall, these simulations suggest that in all but one scenario, the risks of non-adjunctive CGM use are similar to SMBG, and CGM offers additional benefits. Risks associated with an occasional increase in hypoglycemic events for pediatric subjects with CGM are mitigated by the presence of alerts. In the highest risk population, patients with impaired hypoglycemia awareness, CGM performs better than SMBG in reducing severe hypoglycemia without an increase in hyperglycemia.

Table 8: Summary of Outcomes

Glycemic Outcome	Summary of Benefits and Risks of CGM-based Decision Making
Average Event Rate and Time spent below 50 mg/dL	Benefits CGM reduced the rate of events below 50 mg/dL by 19% for adults and 5% for pediatrics with mixed hypoawareness, with the greatest decrease seen in the impaired hypoawareness group (40% reduction for adults and 45% reduction in events for pediatrics). The average duration of events below 50 mg/dl was reduced by 4 minutes in adults and 7 minutes in pediatrics for the mixed hypoawareness group. The impaired hypoawareness group saw average event duration reductions of 7 minutes in both adults and pediatrics. No difference was seen for median time below 50 mg/dL for the mixed hypoawareness group (median time of 0 minutes/day). CGM reduced the time spent below 50 mg/dL for the impaired hypoawareness groups for both adults and pediatrics, with an increase in the number of subjects experiencing <5 minutes/day below 50 mg/dL. Risk The average rates of events below 50 mg/dL were higher for pediatric subjects in both hypoawareness groups only on day 1 of sensor wear but the average event duration was noticeably reduced for all cohorts, indicating that CGM alerts and the alarm are an effective mitigation.
Time spent between 70-180 mg/dL	Benefit CGM resulted in slightly more time in the target glucose range for both awareness groups for both adults and pediatrics. Risk No risks were identified.
Time spent above 250 mg/dL	Benefit CGM decreased the amount of time spent above 250 mg/dL for both adults and pediatrics. Hypoglycemia awareness did not have any impact on this result. Risk No risks were identified.

1.4.2 MEAL DOSING SIMULATION

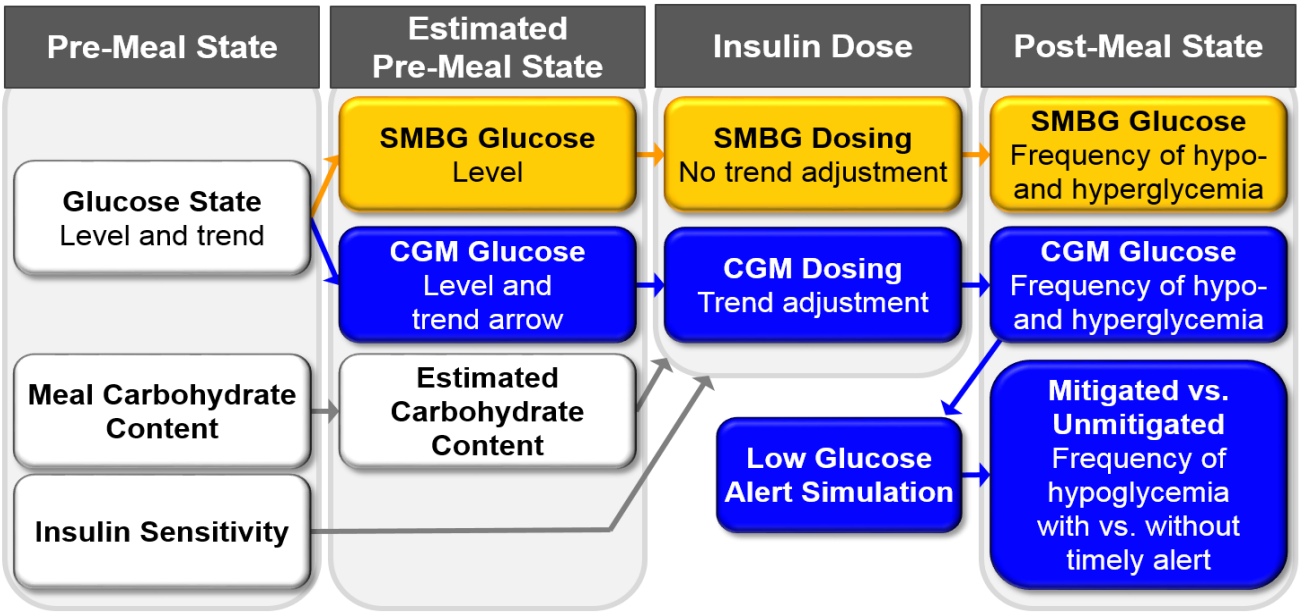
1.4.2.1 Background and Methods

The meal dosing simulation was designed to identify specific conditions that may demonstrate increased risk for non-adjunctive use. The simulation was designed to be simple in order to focus on specific potential risks and differences between CGM and SMBG. It represents a single decision (not two-weeks of wear) made using CGM versus one made using SMBG. Both the SMBG-based and CGM-based insulin doses were determined using the standard bolus equation; however, the CGM-based dose was adjusted up or down based on rising or falling glucose (i.e., trends and trend arrows). That single decision was repeated to assess the influence of various parameters using a simple Monte Carlo simulation method. Parameters evaluated include physiological parameters such as insulin sensitivity, user behavior errors such as errors in estimation of carbohydrates, and conditions that could impact CGM performance such as reduced calibration frequency or calibrating with a less accurate meter.

Data for this simulation came from CGM and SMBG data obtained during the clinical testing phase of the Software 505 algorithm trial (the algorithm used in the Dexcom G5 Mobile System). The simulations compared a single meal-time insulin dosing decision based on a CGM glucose reading (and trend) to a dosing decision based on a SMBG point value. A baseline simulation was initially run to establish the risk of hypoglycemia and hyperglycemia for both SMBG and CGM under typical dosing conditions. Then specific parameters were modified to understand their impact on the hypoglycemic or hyperglycemic risk profiles compared to baseline. Since hypoglycemia poses the greatest acute risk to a subject, the following results focus on the hypoglycemia risk.

Figure 5 provides an overview of this simulation. White boxes indicate components that are common to simulations of dosing based on both SMBG and CGM measurements. Yellow boxes are specific to dosing simulations using SMBG measurements, and blue boxes are specific to dosing simulations using CGM measurements.

Figure 5: Meal Dosing Simulation Overview



Hypoglycemia: <70 mg/dL; Hyperglycemia: >180 mg/dL

Simulation steps included the following:

1. Sample input parameters (SMBG, CGM value and trend, carbohydrates, insulin sensitivity)
2. Simulate CGM and SMBG measurements (estimated pre-meal state)
3. Calculate insulin doses based on SMBG and CGM
4. Calculate post-meal glucose level for SMBG and CGM based on the dose error for each (comparison to optimal dose) and the subject's insulin sensitivity
5. Simulate low glucose alerts for subjects with post-meal hypoglycemia (<70 mg/dL) and determine whether they would be likely to mitigate the post-meal hypoglycemia
6. Quantify risk of hypoglycemia and hyperglycemia by calculating the fraction of simulated subjects with post-meal glucose >180 mg/dL (indicating hyperglycemia risk) and the fraction with post-meal glucose <70 mg/dL that did not receive a CGM low glucose alert within ±15 minutes of hypoglycemia onset (indicating hypoglycemia risk), for the two doses (not shown in Figure 5).

Each simulation consisted of 50,000 simulated subjects with randomly drawn pre-meal blood glucose values and rates of change, insulin sensitivity, and meal carbohydrate contents. CGM and SMBG measurements were then simulated using models of measurement error derived from clinical study data, and carbohydrate estimates were simulated by applying a model of carbohydrate counting errors based on published data (Brazeau et al, 2013).

For each simulated subject, the insulin dose required to cover a meal was calculated based on the carbohydrate estimate and the simulated CGM or SMBG readings (including trend for CGM), using the standard bolus equation and a published dose adjustment to account for glucose rate of change (DirecNet Study Group, 2008). The resulting doses were compared to an optimal dose, calculated from the same bolus equation, using the error-free pre-meal glucose level and rate of change and the actual amount of carbohydrates in the meal.

Errors in doses calculated from CGM and SMBG (differences from the optimal dose) were then used to calculate post-meal glucose levels for each treatment group, based on the virtual subject's insulin sensitivity. For CGM-based treatment, CGM low glucose alerts were also simulated to determine what fraction of the post-meal hypoglycemia cases would potentially be mitigated by an alert; alerts provided within ± 15 minutes of dropping into hypoglycemia were considered effective mitigation.

Simulated outcomes were quantified in terms of the percentage of simulated subjects with post-meal hypoglycemia (<70 mg/dL), before and after considering the effect of low glucose alerts, and the percentage with post-meal hyperglycemia (>180 mg/dL). A more complete description of simulation methods is provided in Appendix 13.1.

This model was designed to be simplistic and, therefore, has some assumptions and limitations:

- The dosing simulation did not involve any physiological model. Instead, the deviation between actual and optimal insulin dose was translated into a deviation of post-meal glucose level from target glucose level, and the actual glucose rate of change immediately preceding the post-meal glucose level was assumed to be -1mg/dL/min, unless otherwise specified.
- Subjects were assumed to set a CGM low glucose alert threshold at 70 mg/dL. No hyperglycemia alerts were simulated for CGM.
- There was no error in a subject's estimation of their insulin sensitivity factor (ISF) or insulin to carb ratio (ICR) in the baseline simulation.
- Subjects determining insulin dose based on SMBG were assumed to have no knowledge of their current glucose trend, and therefore calculated an insulin dose as if their glucose rate of change was 0 mg/dL/min.
- Subjects basing decisions on SMBG measurements were assumed to not perform post-meal glucose tests.
- Subjects did not learn from their experience.
- Subjects did not have symptoms of hypoglycemia.

1.4.2.2 Simulated Conditions

For each simulation, the risks associated with determining an insulin dose based on a pre-meal CGM reading (with and without CGM low glucose alerts) were directly compared to the risks associated with dosing based on a pre-meal SMBG measurement. Since hypoglycemia poses the greatest acute risk to a subject, the following results are focused on the hypoglycemia risk.

A single simulation of 50,000 subjects was run for each of the patient and sensor characteristics listed in Table 9. Each condition was simulated by replacing the corresponding baseline input (e.g. fixing insulin sensitivity at a high level or low level rather than drawing from a wide distribution), error model (e.g. changing the magnitude of carbohydrate-counting errors), or behavioral parameter (changing the CGM low alert setting from 70 to 80 mg/dL) with a new value or range of values. The results of each simulation were compared to the baseline simulation to identify which conditions influence risk of CGM-based and SMBG-based dosing.

Table 9: Simulated Conditions to Evaluate Glycemic Risk

Factor	Simulated Condition
Patient Physiology	• Insulin sensitivity (ISF and ICR) • Relationship between ISF and ICR • Errors in insulin sensitivity estimation
User Behavior	• Carbohydrate-counting error • Alert threshold • Erroneous compensation for pre-meal rate of change • Target glucose • Meal size • Calibration frequency
SMBG Performance	• SMBG precision • Systematic SMBG bias • Inaccurate calibration of CGM
Miscellaneous	• Adults vs. pediatrics • Pre-meal glucose level • Day of CGM wear • Correction bolus (lack of meal)

1.4.2.3 Baseline Simulation Results

The baseline simulation reflects results that would be expected in a typical real-world setting by using inputs, error models and behaviors that either reflect the full range of possible conditions, were derived from previous clinical data, or are expected to be typical based on clinical logic. A full list is provided in Appendix13.1.3. However, the baseline simulation assumed an aggressive target glucose level of 100 mg/dL to maximize the risk of hypoglycemia for CGM-based decisions.

Figure 6 depicts the hypoglycemia risk for the baseline simulation. Lower lines on the graph indicate lower overall risk for hypoglycemia and flatter lines indicate more consistent results across the range of

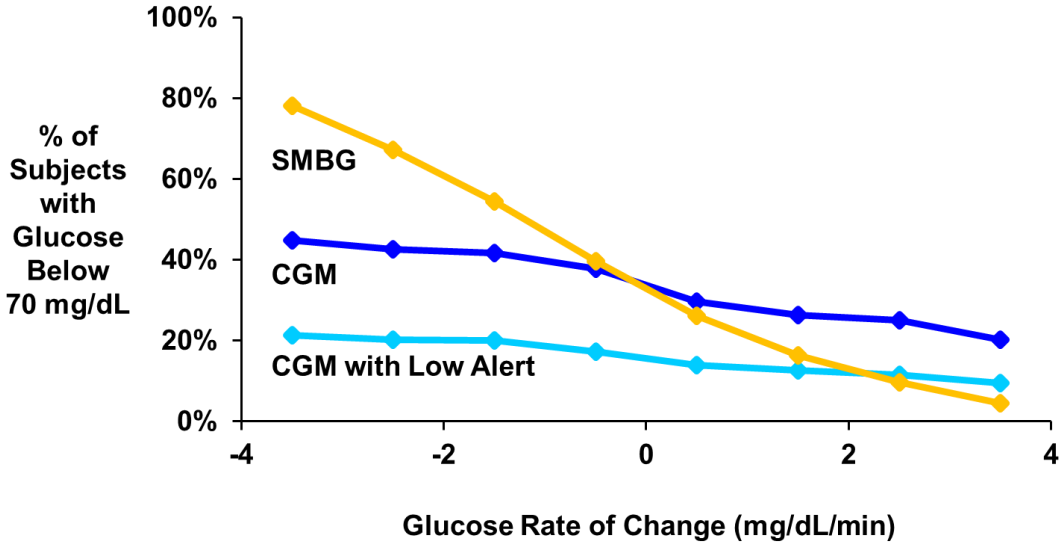
possible pre-meal glucose rates of change. The figure shows that SMBG-based dosing risks were highly dependent on pre-meal glucose rate of change. In contrast, CGM-based dosing risks were far less dependent on pre-meal glucose rate of change, as evidenced by a flatter line across the various glucose rates of change. The consistent reduction in hypoglycemia risk from CGM-based dosing when adding low glucose alerts, (light blue vs. dark blue line), demonstrates that CGM alerts and alarms effectively mitigate much of the hypoglycemia risk, across the full range of pre-meal glucose rates of change.

For both SMBG and CGM-based dosing, risk of hypoglycemia was highest for rapidly falling glucose rates of change, though CGM, especially with low alerts, had significantly less risk than SMBG. This demonstrates that the CGM low glucose alert and alarm effectively mitigate hypoglycemia risk in this situation.

At a high positive rate of change, CGM users increase their insulin dose and take more insulin than patients using SMBG to determine their insulin dose. This results in a greater risk of hypoglycemia, but alerts reduced the risk from the increased insulin dose to a level that was similar to SMBG-based dosing.

As expected, risk of hyperglycemia was higher for larger positive pre-meal rates of change (data not presented) for both CGM and SMBG.

Figure 6: Hypoglycemia Risk in Baseline Condition



Lines depict the percent of simulated subjects whose meal doses resulted in post-meal glucose below 70 mg/dL (indicating risk of hypoglycemia) for each pre-meal glucose rate of change. The light blue line shows the percent of subjects with post-meal hypoglycemia, after excluding subjects that received a low glucose alert within 15 minutes of hypoglycemia onset.

1.4.2.4 Simulation Results—Biggest Contributors to Hypoglycemia Risk

Table 10 includes the risks identified compared to baseline.

Table 10: Risks Identified with CGM Use

Risk Level Compared to Baseline	Simulated Conditions
Increased Risk for Both CGM and SMBG	Increased errors in insulin sensitivity information Increased carbohydrate counting errors Lower target glucose Larger meals Systematic SMBG bias
Unique Risk for CGM only	Incorrect use of trend information Setting alert thresholds at low glucose values Decreased calibration to 1 time every 2 days

Simulations of a variety of different meal-time dosing conditions demonstrated that the biggest contributors to hypoglycemia risk were:

- Incorrect carbohydrate estimates in meals
- Incorrect estimates of individual insulin sensitivity

These risk factors were not related to device errors but to user behaviors and had a similar impact to the risk with both SMBG-based and CGM-based dosing. Setting a lower glucose target for insulin dosing and consistently high or low SMBG values (systematic SMBG bias) also resulted in an increased risk for both CGM and SMBG.

1.4.2.5 Simulation Results—Hypoglycemia Risk Scenarios Unique to CGM

For most of the conditions simulated, risks were similar between CGM-based dosing and SMBG-based dosing. However, CGM showed increased risk relative to the baseline simulation in three scenarios that were unique to CGM. These unique risks involved:

- Incorrect use of trend information
- Setting low alert thresholds at too low of a glucose value
- Only calibrating the CGM once every two days (instead of the recommended two calibrations per day)

Not surprisingly, the risks for users who ignore trend information and just use the CGM glucose value when determining an insulin dose are very similar to SMBG, though the use of CGM alerts reduced the

risk in all glucose rates of change. This scenario does highlight potential residual risk from over-zealous meal insulin adjustments based on rate of change.

The results suggest that setting the low alert threshold to a higher glucose level increases the likelihood that hypoglycemic events caused by mealtime insulin overdose would be mitigated by CGM alerts. This result is consistent with a recently published analysis of the impact of low glucose alert threshold on alert timing relative to hypoglycemia onset (Peyser et al, 2015).

The recommended calibration schedule for the Dexcom G5 Mobile Systems is two calibrations at the two- hour startup time and one calibration every following twelve hours. Calibration frequencies of one per day had little impact on risk, but further reduction in calibration to only once per two days (i.e., every other day) resulted in increased risk of post-meal hypoglycemia. This risk is mitigated by providing prompts to the user to calibrate the device every twelve hours. Both the receiver and app provide these prompts, reminding the user to calibrate.

1.4.3 SUMMARY OF SIMULATIONS

The combination of the two-week simulation study and the single meal dosing simulation provided a comprehensive assessment of the safety and effectiveness of the Dexcom G5 Mobile System. The simulations highlighted a few potential risks of using CGM to make treatment decisions but generally demonstrated that the risks of non-adjunctive CGM are similar to or reduced relative to SMBG-based treatment decisions. Using CGM for making diabetes treatment decisions resulted in improved glycemic outcomes, with a reduction in time spent above 250 mg/dL, slightly more time in the target glucose range, and equivalent or less time below 50 mg/dL. The average rate and average duration of events below 50 mg/dL was also reduced. Pediatric subjects may see an increase in the number of events on the first day of sensor wear but the average event duration is reduced due to the CGM low glucose alert and alarm. Infrequent CGM calibration once every two days also resulted in potentially higher risk as did incorrect dosing due to the CGM trend arrow, but the risks identified can be mitigated by the CGM alerts and alarm and on-screen prompts. The simulations thus demonstrated that non-adjunctive CGM use is safe and effective.

1.5 PATIENT AND CLINICIAN EDUCATION

The clinical evidence for the adjunctive use of CGM and the simulations supporting non-adjunctive use show that CGM can be used safely to make treatment decisions. Therefore, Dexcom plans a product training program to inform users of the appropriate ways to optimize their CGM-based treatment decisions and when users should not use CGM for treatment decisions using existing information from the current, commercial G5 Mobile System instructions and revised information for CGM-based treatment decision (Table 11).

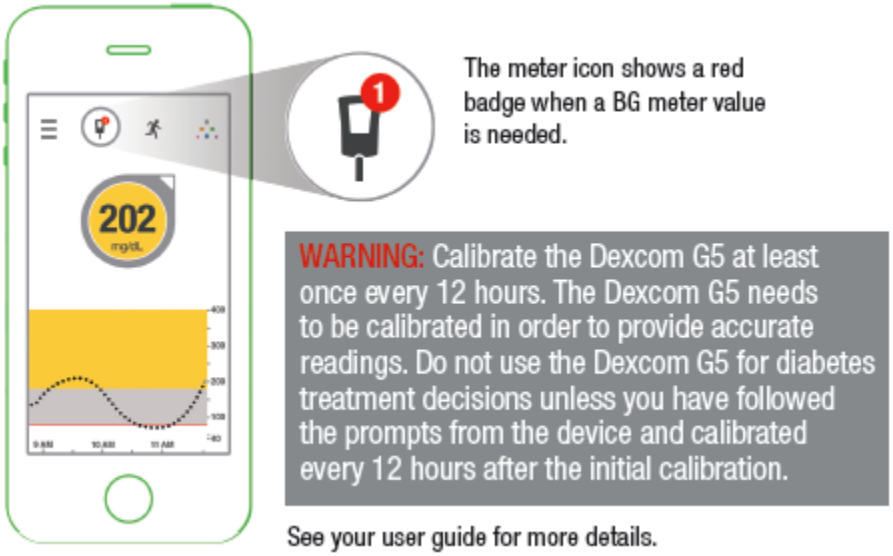
Table 11: Key Training Information

Revised Key from Current, Commercial Instructions Relevant to CGM-based Treatment Decisions	New Keys for Making CGM-based Treatment Decisions	New Information When SMBG is Required/ When Not to Treat with CGM
Calibration every twelve hours	CGM reading Trend arrow Calibration with SMBG every twelve hours	Calibration Symptoms do not match CGM readings Taking acetaminophen No CGM reading No arrow

1.5.1 REVISED KEY INFORMATION FROM CURRENT, COMMERCIAL INSTRUCTIONS

The revised instructions remain very similar to the existing instructions. One instruction particularly relevant to CGM-based treatment decisions is the requirement to calibrate every twelve hours. Calibration helps provide accurate CGM readings, and this accuracy is important for CGM-based treatment decisions. Dexcom has retained the existing instructions on calibration with slight modifications related to non-adjunctive use (Figure 7).

Figure 7: Example of Calibration Warning in the Getting Started Guide



1.5.2 NEW KEY INFORMATION IN REVISED INSTRUCTIONS

The revised instructions explain that in order to make CGM-based treatment decisions the user needs (Figure 8):

- A CGM reading (number)[5]
- A trend arrow

The CGM reading provides a point glucose value, like an SMBG value, on which to base treatment decisions. The arrows serve two purposes. First, their presence indicates that the system has adequate information to rely on the reading. This means the system has a history of consistent readings that suggest the sensor is accurate and not "noisy." Second, their presence provides additional information to inform treatment decisions, such as the speed and direction of glucose change (e.g., rapidly increasing versus remaining stable). Note that there are situations where an arrow is not present but a CGM reading is present. In these situations, there is adequate information to rely on the CGM reading for alerts and trending, but there is inadequate information to make CGM-based treatment decisions.

[5] "Number" is the layman's term used in the instructions to help users remember a CGM reading is required. The CGM reading is the number in units of mg/dL.

Figure 8: Screenshots from Interactive Training Tutorial

Top: CGM reading (number) and arrow. Middle: reading and arrow needed to make treatment decision (eating). Bottom: absence of arrow indicates SMBG for treatment decisions.

The instructions inform the user that SMBG is still required:

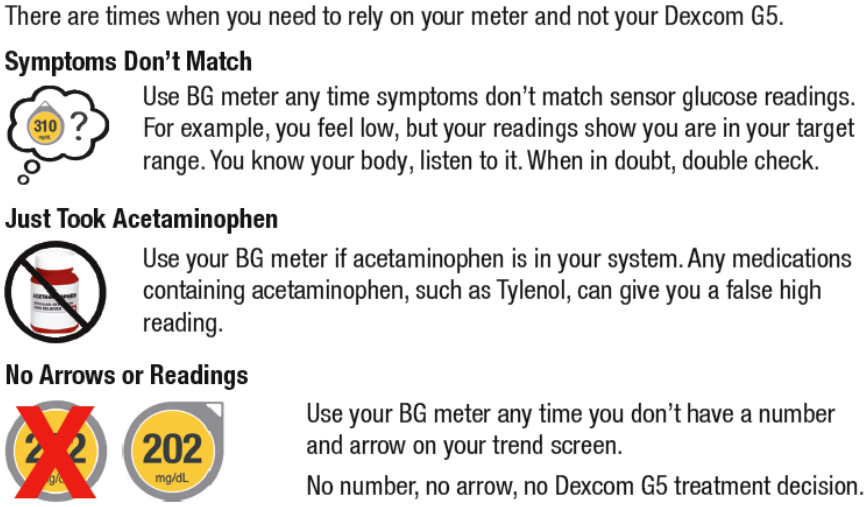
- For calibration; and
- At times when the CGM information is incomplete or potentially unreliable

To clarify these times when the CGM information is incomplete or potentially unreliable, the instructions specifically emphasize three instances where users should not treat based on CGM readings (Figure 9):

- When symptoms or expectations do not match the CGM reading
- When the user has taken acetaminophen
- When a CGM reading is missing or when a trend arrow is missing

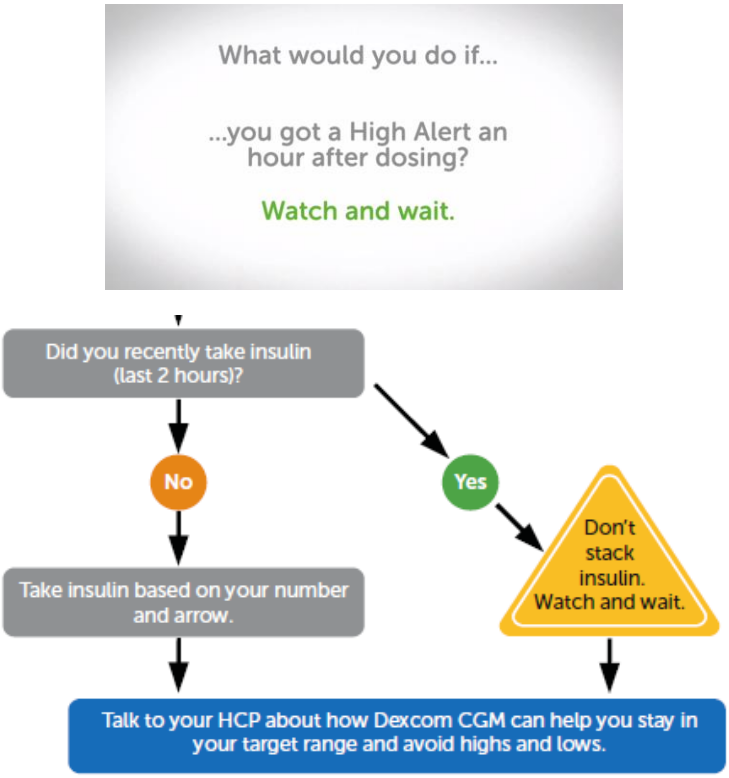
Although there might be enough information to use CGM alerts and trending in these three instances, there is inadequate information to make CGM-based treatment decisions.

Figure 9: Getting Started Guide Showing When Not to Use CGM for Treatment Decisions



Since a patient could use the CGM information to dose insulin, the instructions also inform the user about the risks of stacking insulin (Figure 10). Insulin stacking occurs when a user administers an insulin bolus while the previous insulin bolus is still active, which increases risk for hypoglycemia.

Figure 10: Screenshot from Interactive Tutorial (top) and Getting Started Guide (bottom) Regarding Stacking Insulin



1.5.3 FORMAT OF REVISED INSTRUCTIONS

Dexcom revised the G5 Mobile System's IFU to focus on the important information related to CGM-based treatment decisions and remove redundancy. The instructions are the same for naïve and experienced CGM users, and both parties were tested (Section 9).

Dexcom plans to provide a product training program for patients and healthcare professionals (Table 12).

Table 12: Methods of Training

Product Instructions for Use	Getting Started Guide (printed in receiver kit) Interactive Tutorial (video on USB card in receiver kit and online) User Guide (electronic or printed by request) Brief package inserts in sensor kit and receiver kit
In-app Training	Users are required to view screens during initial setup of Dexcom G5 Mobile App
Dexcom Patient Care one-on-one and group patient training	Webinars Phone, email, text communication
Additional web-based materials	Case-based examples
Education for healthcare professionals	Account training Printed materials Online materials

Dexcom's comprehensive training strategy includes five main methods:

1. **Product IFU** will be shipped to each patient in the receiver box and available online.
    a. The primary product instructions include the Getting Started Guide and the interactive tutorial, both of which were validated through the Human Factors Studies for either one-on-one training or self-training (see Section 9). A copy of these documents is provided in the briefing materials; the tutorial is provided on disc. Reviewers who would like to view only the new section of the tutorial focused on CGM-based treatment decisions may use the Menu button at the top right to scroll to "Using CGM for Treatment Decision" and "Treatment Decisions Video" followed by three case-based questions to test users' understanding of CGM-based treatment decisions.
    b. An electronic user guide/e-book will be available as a comprehensive product reference. Users can download the user guide or request a free printed copy by mail or through an online request form.
    c. Brief package inserts will be included in the receiver box and the sensor boxes. These inserts concisely describe the most important details of the keys for treating with CGM (reading and arrow) and when not to treat with CGM. The inserts direct users to where

they can find the full training materials. The inserts are concise and designed to grab the attention of users who might otherwise decline to train.

2. The G5 Mobile app includes **in-app training**. After a user downloads and launches the app for the first time, the in-app training begins, requiring each new patient to view the in-app training.
3. Dexcom offers remote product training with the **Patient Care Team**, a group of certified diabetes educators (CDEs) available to help patients get started and answer product education questions. The Patient Care Team reaches out to known[6] new users by phone call, email or text within three days of the initial shipment and contacts known new users again at specified intervals (2 weeks, 1 month, 3 months). Users may call Patient Care directly as well.
4. Dexcom will provide additional **web-based** materials including case-based examples.
5. Finally, **education and tools for healthcare professionals** will be available to help facilitate ongoing training for the healthcare professionals. These tools will closely mirror the education developed for patients. In addition, healthcare professionals may view reports provided by the Dexcom CLARITY system (see Section 3.1), which retrospectively identifies patterns and issues in a user's CGM history.

1.5.4 EDUCATION FOR CURRENT USERS

Dexcom plans multiple methods to inform current users who are familiar with CGM that training is available on CGM-based treatment decisions:

- Brief package insert in sensor box
- Email
- Postal mail
- Notifications through G5 Mobile App
- Dexcom website
- Banner ads
- Informing distributors
- Patient Care communications (during inbound calls for other reasons)

The training methods available include all of those described in Section 1.5.3, including the revised interactive tutorial and specialized group training by Dexcom's Patient Care team. To accommodate for users who have changed addresses without informing Dexcom or for those who purchase through a third party, Dexcom will post information on the Dexcom web page and on banner ads and will provide information to distributors. Because every continuing Dexcom customer orders sensors (the disposable component), all sensor boxes will include inserts that describe key information about treatment with

[6] Due to the use of third party distributors and pharmacies, Dexcom may not have immediate knowledge of all new users. All new users (known or unknown) receive a card in their first receiver kit informing them of the Patient Care team and how to contact Patient Care.

CGM. These inserts are designed to be concise in order to grab the attention of users who might otherwise decline to train.

1.6 HUMAN FACTORS USABILITY STUDY

The human factors usability study evaluated the new IFU and pertinent sections of the safety statements for clarity and ability to support safe and effective non-adjunctive use of the Dexcom G5 Mobile System. The study evaluated the efficacy of the two primary methods of training: the Interactive Training Tutorial as the primary training tool for users who choose to self-train at home and the efficacy of the Getting Started Guide when used in conjunction with a health care provider in one-on-one training. Both of these methods are used in the current commercial Dexcom G5 Mobile System. Dexcom revised these to include instructions relevant to making CGM-based treatment decisions and when not to make CGM-based treatment decisions. Three user groups, adults, pediatrics and caregivers of young children with diabetes, were assessed on their retention of critical knowledge related to product labeling. The study included a subset of participants from each user group that did not receive formal training to reflect a worst case scenario where current Dexcom CGM users are informed about the new labeling but do not receive formal training.

The study was conducted on 49 participants, from three user groups: adults, self-managing pediatrics and caregivers (e.g., parents). Participants were tested on six scenarios evaluating their comprehension on three critical risks:

Risks:

1. Using CGM for diabetes treatment decisions without a number[7] and arrow
2. Using CGM for diabetes treatment decisions when symptoms do not match the CGM reading
3. Insulin Stacking

Scenarios:

1. Using CGM values to determine a treatment decision under nominal conditions
2. Risk of insulin stacking with SMBG (insulin stacking occurs when a user administers an insulin bolus while the previous insulin bolus is still active, which increases risk for hypoglycemia)[8]
3. User's symptoms do not match CGM value
4. Using CGM values to determine a treatment decision with an error message present
5. Risk of insulin stacking with CGM
6. Using CGM values to determine a treatment decision when no trend arrow is present due to potentially inaccurate sensor glucose readings

[7] "Number" is the layman's term used in the instructions to help users remember a CGM reading is required. The CGM reading is the number in units of mg/dL.
[8] This SMBG-based scenario was provided as a baseline to understand insulin stacking related to the current standard of care and is not counted as one of the five CGM-based scenarios.

These scenarios were designed to test users' comprehension of critical knowledge of when they can and cannot use CGM for treatment decisions based on the three risks outlined above.

Based on the usability testing performed in the Summative Usability Study, the critical knowledge is effectively communicated in the training and IFU, and non-adjunctive use risks of the G5 Mobile System are largely mitigated. The results of the study suggest that there are no significant differences between the two formal training methods: self-training and one-on-one training. The 40 participants who received training by either method achieved a high success rate across the five scenarios that relate to risks using CGM for treatment decisions (Scenarios 1, 3, 4, 5, and 6). No failures were observed in naïve users or in users who received self-training with the tutorial. No failures were observed in trained pediatric users. Only one failure by one CGM experienced participant was observed in the CGM-based scenarios; this participant received one-on-one training (Table 13).

Table 13: Overall Efficacy of Training on CGM Errors (40 trained participants; 5 CGM scenarios)[9]

Training Method	Naïve (n=19)	Experienced (n=21)
Self-training with tutorial (n=21)	100% (n=9)	100% (n=12)
One-on-one training (n=19)	100% (n=10)	98%[10] (n=9)

Table 14 shows the three risks identified with non-adjunctive CGM use. Of these three risks, one failure was observed in a scenario where a CGM reading with no arrow was present. The participant, who was a CGM experienced adult and received formal one-on-one training, stated that she would calculate her insulin dose based on a potentially inaccurate CGM reading. Specifically, she stated that she would test her blood sugar with a fingerstick, calibrate her CGM system and determine her insulin dose based on the calibrated CGM value instead of the fingerstick value. In the context of this study, the response is considered a failure; however, as she did state that she would test with her meter her overall behavior is considered low risk.

Table 14: CGM Risks Identified in Trained Users (n=40)

Risks of Using CGM for Treatment Decisions	Response	
	Correct / Total	%
Without a number and arrow	119 / 120	99%
When symptoms do not match CGM reading	40 / 40	100%
Insulin stacking (CGM)	40 / 40	100%

[9] Percentages were calculated based on the overall success rates of the 40 participant who received training on their responses to the 5 tasks related to CGM risks. The scenarios tested in the study that related to risks of using CGM non-adjunctively were mapped to these risks.
[10] Nine participants with 5 CGM scenarios results in 45 tests. One participant failed one scenario, as discussed in section 5.9, resulting in 98% rate for this combination.

A subset of nine participants who did not receive any training achieved a lower success rate across the five scenarios that relate to risks using CGM for treatment decisions. This is not unexpected as these users did not receive any information on when they can and cannot use CGM for treatment decisions. See Table 15.

Table 15: CGM Risks Identified in Untrained Users (n=9)

Risks of Using CGM for Treatment Decisions	**Response**	
	Correct / Total	**%**
Without a number and arrow	24 / 27	89%
When symptoms do not match CGM reading	8 / 9	89%
Insulin stacking (CGM)	9 / 9	100%

There have been concerns about the risks from stacking insulin based on the frequent glucose data and trend information a CGM user would have. Stacking insulin is not unique to CGM use. Importantly, this study confirms the IFU materials are adequate to mitigate insulin stacking from non-adjunctive CGM use.

The results of this study demonstrate that risks of non-adjunctive use are mitigated through training; there were no comprehension-based errors in users who were CGM naïve or who self-trained and only one failure in one user who was CGM experienced and received one-on-one training. The failure observed has low risk to the user as that although she stated she would dose insulin based on a potentially inaccurate CGM value, she did test her blood glucose with a fingerstick.

There remains some residual risk from non-adjunctive use of the device. If patients do not receive or participate in training on non-adjunctive use of the device, they may misunderstand when they can and cannot use the CGM for diabetes treatment decisions. Three participants who were untrained were already using CGM non-adjunctively, one reportedly on the recommendation of their clinician. These participants did not receive adequate instructions on when to use CGM information for treatment decisions and when to rely on a fingerstick. Dexcom cannot provide training to users or clinicians about proper non-adjunctive use without an approved indication for non-adjunctive use. Therefore, this study highlights the need for a non-adjunctive indication. Dexcom plans on conducting outreach to all current users (as described in section 1.5 Patient and Clinician Education) to inform them on when they can and cannot use CGM for treatment decisions upon approval of the new indications for use in the event that they do not receive or choose to decline one-on-one or self-training.

Based on the limitations of SMBG based-decision making and the current non-adjunctive use of CGM by patients without proper training on risks, the potential benefits of using the Dexcom G5 Mobile System in a non-adjunctive manner for diabetes management far outweigh the low residual risk.

1.7 BENEFIT RISK CONCLUSION

On reviewing all of the available information, the benefits of non-adjunctive CGM use to make treatment decisions outweigh the potential risks. Dexcom has assessed the probable benefits and risks of using the Dexcom G5 Mobile System as a non-adjunctive device by considering the potential benefits of using CGM for managing diabetes, the probable risks introduced to the patient population, and additional factors including patient tolerance for risk and availability of alternative treatments or diagnostics. In total, Dexcom conducted a formal risk analysis, conducted a literature review, reviewed existing clinical performance and usability data, conducted a usability study to evaluate the effectiveness of the training materials to mitigate risk, performed simulations analyses for worse-case scenarios to compare risk between insulin dosing based on CGM data and SMBG measurements, and conducted a simulated two-week clinical study to compare the risk of using the Dexcom G5 Mobile System non-adjunctively compared to SMBG.

There is an unmet need with the current standard of care. With the majority of insulin-using patients not meeting the recommended HbA1c targets for glycemic control and many experiencing frequent and severe episodes of hypoglycemia, diabetes management can still be improved. Patients are instructed to make treatment decisions using SMBG devices, although many devices in actual use do not exhibit the accuracy required by FDA due to improper SMBG techniques (e.g., forgetting calibration, not washing hands). Additionally, SMBG is a burden for patients, and most patients do not monitor their blood glucose frequently enough. Although CGM provides mitigations for these SMBG risks, many patients are unwilling to use a device that requires confirmation by a second device. They feel they have no reason to trust CGM if it requires confirmation. A non-adjunctive indication, eliminating the requirement for confirmatory SMBG fingersticks for diabetes management, would increase adoption of CGM, thereby improving glycemic control in patients with diabetes.

Many patients who currently use CGM are already basing their treatment decisions on CGM without confirming with SMBG. However, there are no instructions for these patients regarding how and when to use CGM non-adjunctively. Approving the non-adjunctive indication would allow Dexcom to educate and train users and health care professionals on safe non-adjunctive use.

Dexcom has shown that we can provide safe use of CGM-based treatment decisions. Dexcom performed a two-week simulated validation study that included meal insulin dosing, correction dosing, and hypoglycemic management that showed that non-adjunctive CGM use decreased hypo- and hyperglycemic events and increased the amount of time patients spent in target glucose range. Additionally, Dexcom performed a robust simulation of potential benefits and risks of making meal-time insulin dosing treatment decisions based on CGM data compared with SMBG. In nearly all of the conditions investigated in the simulations report, CGM-based treatment decisions led to fewer unmitigated hypoglycemic events relative to SMBG-based insulin dosing.

Dexcom has also planned a robust and comprehensive product training program to provide users and clinicians appropriate training for non-adjunctive use of the Dexcom G5 Mobile System. Patients and

caregivers will be provided with product instructions, in-app training, and access to a Patient Care Team of certified diabetes educators (CDEs). Educational materials and tools will also be available for clinicians to support their education efforts around CGM and CGM-based treatment decisions.

The Dexcom CGM System has improved accuracy levels over time and offers the additional benefits of glucose trends with rate, direction of change, and alerts and alarms. Based on the current accuracy, the improved glycemic outcomes demonstrated in simulations and the risk analysis of using the CGM non-adjunctively, Dexcom determined that the potential benefits of using Dexcom G5 Mobile System to "replace" fingersticks for diabetes management far outweighs the low residual risk.

2 INTRODUCTION

Dexcom, Inc. is requesting a modification to the Indications for Use of the FDA-approved Dexcom G5 Mobile System. The Dexcom G5 Mobile System is currently approved as an adjunctive therapy to complement, but not replace, information obtained from standard home glucose monitoring devices. The current Indications for Use are provided in Table 16 below.

Table 16: Current Indications for Use for the FDA-Approved Dexcom G5 Mobile System

Current Indications for Use (Adjunctive Use)
• The Dexcom G5 Mobile Continuous Glucose Monitoring (CGM) System is a glucose monitoring system indicated for detecting trends and tracking patterns in persons (age 2 years and older) with diabetes. The system is intended for single patient use and requires a prescription. • The Dexcom G5 Mobile CGM System is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices. • The Dexcom G5 Mobile CGM System aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions. Interpretation of the Dexcom G5 Mobile CGM System results should be based on the trends and patterns seen with several sequential readings over time.

Dexcom is proposing to expand this indication to allow the Dexcom G5 Mobile System to be used for diabetes treatment decisions, removing the need for patients to confirm their CGM reading with a fingerstick reading from a blood glucose meter prior to treating. Treatment decisions include daily choices made by people with diabetes, such as determining an insulin dose, ingesting carbohydrates, or assessing when to wait before dosing or eating. Data to support this expanded use includes clinical data using the Software 505 algorithm found in the Dexcom G5 Mobile System and computer simulations that model clinical outcomes of non-adjunctive use. The modified Indications for Use are shown in Table 17 below.

Table 17: Proposed Modification Indications for Use

Proposed Indications for Use (Non-Adjunctive Use)
• The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) is a glucose monitoring system indicated for the management of diabetes in persons age 2 years and older. The Dexcom G5 is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. • Interpretation of the Dexcom G5 results should be based on the glucose trends and several sequential readings over time. The Dexcom G5 also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. • The Dexcom G5 is intended for single patient use and requires a prescription.

There are no other changes to the approved device (P120005/S033, approved 8/19/2015). With the proposed indication, the Dexcom G5 Mobile System will still require calibration with SMBG measurements when a new sensor is inserted and every 12 hours. Additionally, the system remains contraindicated while taking medications that contain acetaminophen. The key safety statements are included below. The proposed Indications for Use and Safety Statements are available in the Getting Started Guide included in the briefing materials.

- Failure to use the Dexcom G5 and its components according to the instructions for use and all indications, contraindications, warnings, precautions, and cautions may result in you missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury. If your glucose alerts and readings from your Dexcom G5 do not match your symptoms or expectations, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions. Seek medical attention when appropriate.
- Do not ignore symptoms of low or high glucose. If your glucose alerts and readings do not match your symptoms or expectations, you should obtain fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions or seek immediate medical attention.
- If your Dexcom G5 does not display a sensor glucose reading and an arrow, or if you are getting inaccurate or inconsistent readings, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions.
- Calibrate the Dexcom G5 at least once every 12 hours. The Dexcom G5 needs to be calibrated in order to provide accurate readings. Do not use the Dexcom G5 for diabetes treatment decisions

unless you have followed the prompts from the device and calibrated every 12 hours after the initial calibration.

- Taking medications with acetaminophen while wearing the Dexcom G5 may inaccurately raise the glucose readings generated by the Dexcom G5. The level of inaccuracy depends on the amount of acetaminophen active in your body and is different for each person. Do not rely on continuous glucose monitoring (CGM) data produced by the Dexcom G5 if you have recently taken acetaminophen.

3 OVERVIEW OF THE DEXCOM G5 MOBILE CGM SYSTEM

3.1 DESCRIPTION OF DEVICE: SENSOR, TRANSMITTER, RECEIVER, AND MOBILE APP

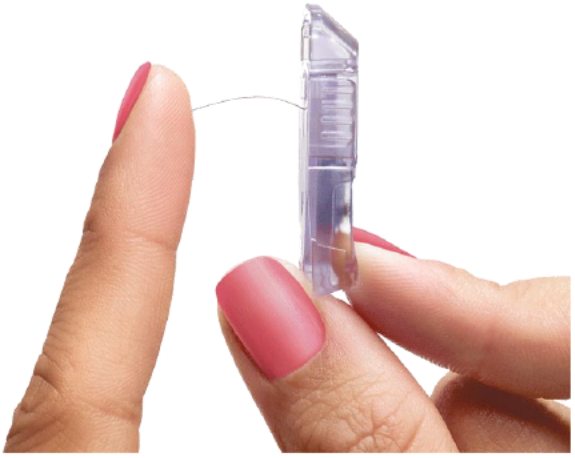
The Dexcom G5® Mobile Continuous Glucose Monitoring (CGM) System (Dexcom G5 Mobile System) is an FDA-approved device (P120005/ S033) designed to provide continuous measurement of interstitial glucose concentrations over a 40-400 mg/dL range for people with diabetes. The device is small and portable and displays glucose values, trends, and rates of change to patients in real time with up to 288 glucose readings per day. The device also has a built-in alarm system to alert patients when glucose levels reach high or low thresholds. The Dexcom G5 Mobile System is intended for single patient use at home and requires a prescription. The system consists of a sensor, transmitter, receiver, and mobile app (Figure 11).

Figure 11: Dexcom G5 Mobile CGM System

The sensor (Figure 12) is minimally invasive and measures glucose concentrations in the interstitial fluid. The sterile sensor is inserted into the subcutaneous tissue of the abdomen for adult patients and abdomen or upper buttocks for pediatrics. The sensor can be worn for up to seven days and is adhered to the skin with an adhesive patch.

The sensor consists of a metal wire that is coated with polymer membranes. The sensor contains glucose oxidase which reacts with glucose in the interstitial fluid to produce hydrogen peroxide. This reaction generates an electrical current proportional to the ambient glucose concentration in the interstitial fluid of the subcutaneous tissue surrounding the sensor. The electrical current produced by the sensor is measured using the Dexcom G5 Mobile transmitter, worn over the sensor.

Figure 12: Dexcom G5 Mobile Sensor



The transmitter (Figure 13) is lightweight, reusable for up to three months, and water resistant, allowing for use during bathing or swimming. The transmitter samples the electrical current produced by the sensor and converts these readings into glucose values using an onboard algorithm.

The transmitter contains wireless Bluetooth® technology and communicates bidirectionally over a secured transmission to the display device. The transmitter sends glucose data at regular five minute intervals to the display device and also receives glucose calibration information that is entered on the display device.

Figure 13: Dexcom G5 Mobile Transmitter

The Dexcom G5 Mobile System offers two visual display options for users, a receiver and Apple iOS© compatible mobile app. The receiver is a small hand-held device with a rechargeable battery. The receiver is provided with every new Dexcom G5 Mobile System and has a one-year warranty. In addition to the receiver, the mobile app offers an alternative user interface for patients with an Apple iOS device. For mobile app users with an Apple Watch®, glucose information can also be displayed on the watch. The receiver and mobile app communicate with the transmitter wirelessly via Bluetooth® technology. Both devices display current glucose readings, trends, and rates of change in real time and can be configured to show glucose data from the last one, three, six, 12, or 24 hours. The figures below show sample display screens from the receiver (Figure 14) and mobile app (Figure 15). Each "dot" on the trend graph represents a sensor glucose reading reported every five minutes. The current glucose reading is indicated by the number at the top of the screen. Trend arrows are shown next to the glucose reading and indicate the direction and rate of change in glucose values over the last 15-20 minutes. Glucose trends are calculated using a weighted average of sequential glucose readings over time.

Figure 14: Dexcom G5 Mobile System Receiver Display

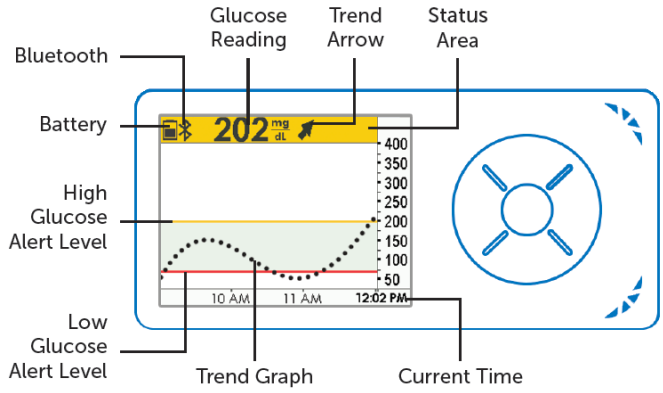


Figure 15: Dexcom G5 Mobile System App Display

Trend arrows inform users of seven different scenarios in changing glucose: constant, slowly rising, rising, rapidly rising, slowly falling, falling, and rapidly falling glucose. All seven potential scenarios are defined in Table 18. The Dexcom G5 Mobile System will only display the trend arrow if a sufficient number of sequential glucose values are obtained to calculate the trend.

Table 18: Definitions of Trend Arrows

App	Receiver	What your glucose is doing
		Glucose is steady. Not increasing/decreasing more than 1 mg/dL per minute or up to 15 mg/dL in 15 minutes.
		Glucose slowly rising 1-2 mg/dL each minute or up to 30 mg/dL in 15 minutes.
		Glucose rising 2-3 mg/dL each minute or up to 45 mg/dL in 15 minutes.
		Glucose rapidly rising more than 3 mg/dL each minute or more than 45 mg/dL in 15 minutes.
		Glucose is slowly falling 1-2 mg/dL each minute or up to 30 mg/dL in 15 minutes.
		Glucose is falling 2-3 mg/dL each minute or up to 45 mg/dL in 15 minutes.
		Glucose is rapidly falling more than 3 mg/dL each minute or more than 45 mg/dL in 15 minutes.
N/A	No arrow	System can't calculate the speed and direction of your glucose change.

In addition to glucose trends, the visual display device indicates thresholds for high and low glucose, shown on the display screen in yellow and red, respectively (Figure 14). In consultation with healthcare professionals, patients can adjust target glucose thresholds and set high and low glucose alerts to warn against glucose excursions. The Dexcom G5 Mobile System also has a non-configurable low glucose alarm set at 55 mg/dL. This urgent low alarm cannot be turned off by the user and provides an additional warning against hypoglycemia. In addition to glucose excursions, the device also alerts patients of important system conditions, such as signal loss, the end of the sensor session, or the need to calibrate.

The system alerts and alarms are produced by the receiver and/or mobile app. In the event an alert or alarm is triggered, the device will vibrate or produce an audible sound. The system continues to alert/alarm until the user acknowledges the alert on the user interface.

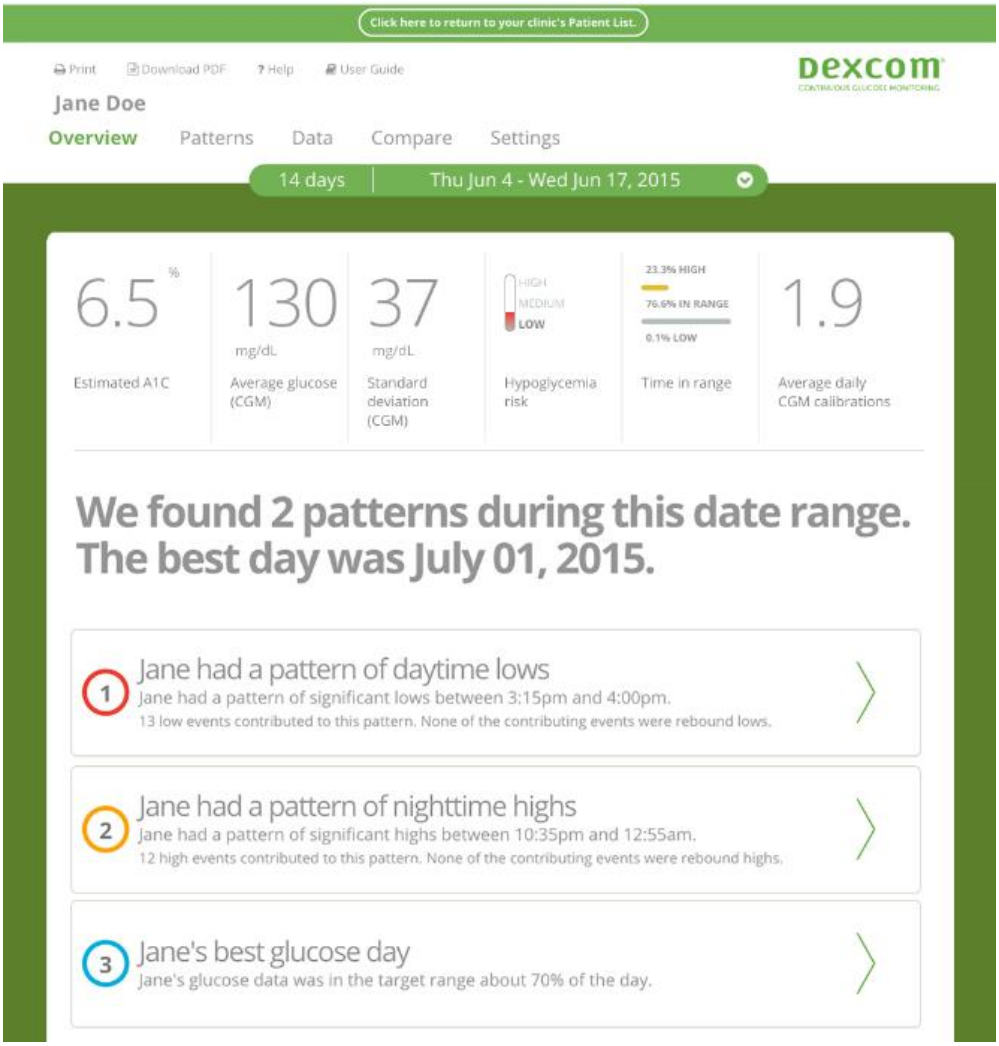
The Dexcom G5 Mobile System must be calibrated with capillary blood glucose values obtained from an FDA-cleared blood glucose meter. Calibration with a blood glucose meter is required to align sensor readings from the interstitial fluid to capillary blood glucose values. Two initial calibrations are required two hours after inserting a new sensor and subsequent calibrations are required every 12 hours from the last time a calibration was entered. The display device prompts users when calibrations are required. Calibration values are entered manually within the user interface of the receiver and/or mobile app. The device's algorithm analyzes calibration values and checks for erroneous blood glucose values, which could result from meter or use error. If the system detects that the blood glucose value is an outlier, the system prompts the user to take an additional fingerstick reading and enter a new calibration value. After the blood glucose values used for calibration are evaluated, they are weighted as part of a rolling average and used by the proprietary algorithm (Software 505) to determine the glucose value sent to the display device.

In addition to displaying real time glucose data to users, the Dexcom G5 Mobile System offers several other features to aid in diabetes management, including a sharing feature and diabetes management software. The Dexcom G5 Mobile App provides connectivity to the Dexcom Share Service (Figure 16), offering patients the ability to share their CGM data wirelessly with up to five friends and family in real time, if they choose. This is especially useful for parents and other caregivers. Once a user, or Sharer, activates the Share feature in their Dexcom G5 Mobile App, the mobile device transfers glucose readings to the Dexcom Share Cloud using either Wi-Fi or a cellular data plan. The sensor glucose readings are then sent from the Dexcom Share Cloud to the mobile device for the Follower, the person remotely monitoring the user’s glucose, via Wi-Fi or cellular data. Using a mobile app on their Apple or Android smart phone, the Follower can receive high and low glucose alerts and monitor trend information from the Sharer. This information can also be displayed on a Follower’s Apple Watch. Dexcom Share is a secondary notification feature and diabetes treatment decisions should not be based upon this feature.

Figure 16: Dexcom G5 Mobile System Share Feature

The Dexcom G5 Mobile system also offers the ability for patients and healthcare professionals to review historical CGM data through the Dexcom CLARITY™ Diabetes Management Software. Dexcom CLARITY is a web-based service where users and healthcare professionals can evaluate CGM patterns over time. The software also provides summary reports, which include average glucose, frequency of calibrations, and patterns of low and high glucose. Healthcare professionals can use the retrospective information presented in Dexcom CLARITY to modify their recommendations for a patient's diabetes management plan. Figure 17 below provides a sample report from the Dexcom CLARITY™ Software.

Figure 17: Dexcom CLARITY™ Sample Summary Report for Healthcare Provider



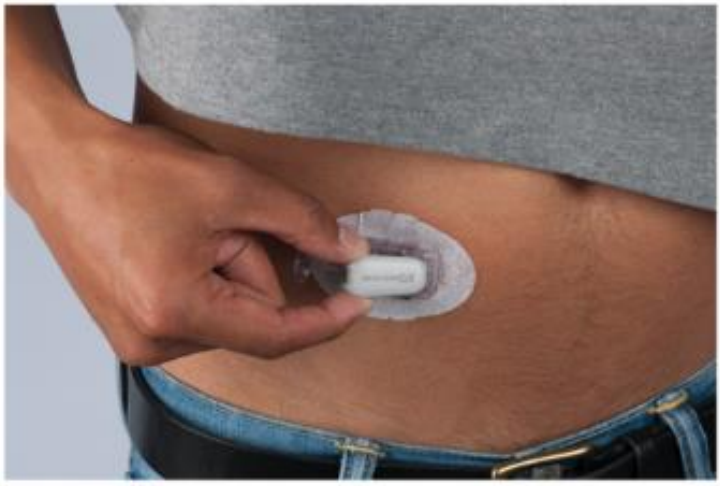
3.1.1 GENERAL OVERVIEW OF SYSTEM OPERATION

The sensor is inserted by the patient using a single-use applicator. After washing hands, the user removes the applicator from the sterile pouch and cleans the insertion site on the abdomen or upper buttocks (pediatrics) with an alcohol wipe. The user then removes the adhesive backing of the sensor pod and secures the sensor pod horizontally on the skin using the medical grade adhesive patch. After the sensor pod is adhered to the skin, the user inserts the sensor by pressing down on the white plunger of the applicator (Figure 18). This deploys the 26-gauge needle contained within the applicator and inserts the sensor just below the skin. The needle is then retracted back into the applicator and the applicator is removed from the sensor pod, leaving behind the sensor, which is held in place by the sensor pod. The sensor can be worn for up to seven days, after which the sensor and sensor pod are replaced.

Figure 18: Dexcom G5 Mobile Sensor Insertion

After inserting the sensor, the user snaps the transmitter into the sensor pod, forming a watertight seal between the sensor and transmitter (Figure 19).

Figure 19: Dexcom G5 Mobile Transmitter Seated in the Sensor Pod and Worn Over the Sensor



Following insertion of the transmitter, the user starts the sensor session using the receiver, mobile app, or both. As the sensor adjusts to the body, there is a two-hour warmup period in which sensor values are not displayed to the user. At the end of this warmup period, the user calibrates the device by taking two fingerstick readings with a blood glucose meter and entering the values on the receiver or mobile app. After calibration, sensor glucose values are displayed to the user every 5 minutes. Users can access their glucose values on demand on either the receiver or mobile app during the wear period. Every 12 hours, the device will notify the user to calibrate using a glucose value from their blood glucose meter. Alerts and alarms will notify the user of any high or low glucose values during use.

As the device wear period approaches seven days, the system will repeatedly alert the user that the sensor session is about to end. Once a sensor session is stopped at the end of seven days, the user removes the adhesive patch with the sensor, sensor pod, and transmitter attached. The transmitter is then removed from the sensor pod and re-used for the next sensor insertion. When inserting a new sensor, the user should insert the sensor at a different insertion site from the previous sensor.

3.1.2 RISKS OF USING THE DEXCOM G5 MOBILE SYSTEM

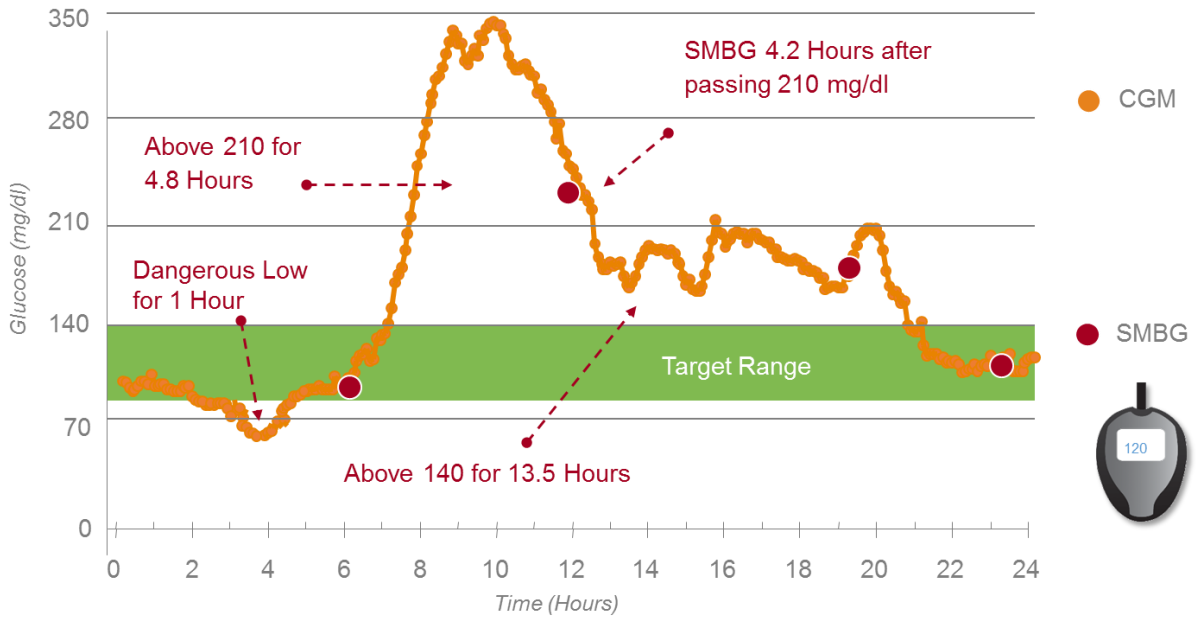
The safety of the minimally invasive Dexcom G5 Mobile System has been established through clinical studies and post-market surveillance. The risks of using the system are low but may include pain or discomfort, bleeding, bruising, scarring, or a hematoma during sensor insertion or removal. Local infections at the insertion site are extremely rare. Users may experience inflammation, irritation, itching, or skin discoloration from wearing the adhesive patch. There are also potential risks due to missed alerts, false alerts, and false high and low glucose readings which could lead to hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar), respectively. Failure to detect hypoglycemia or hyperglycemia or erroneous insulin dosing determination could also result if the CGM readings are inaccurate or the system inaccurately calculates the rate of change of glucose and the user is relying on or using the rate of change information for their diabetes management. The Dexcom G5 Mobile System should be removed prior to any Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Taking medications with acetaminophen (such as Tylenol®) may also falsely raise sensor glucose readings; the amount of the inaccuracy depends on the acetaminophen level.

4 ADJUNCTIVE USE OF CGM

4.1 WHAT DOES ADJUNCTIVE CGM USE MEAN FOR PATIENTS?

The Dexcom G5 Mobile System is FDA-approved as an adjunctive device to complement information obtained from SMBG. Along with routine SMBG, the Dexcom G5 Mobile System provides users with additional information for diabetes management such as the direction and rate of change in glucose. Most patients check their SMBG on a fixed schedule such as before meals, at bedtime, and additionally when needed (Figure 20). CGM complements information obtained from SMBG allowing users to detect glucose excursions between fingerstick readings. Figure 20 demonstrates the utility of the Dexcom G5 Mobile System. A patient's fingerstick readings are indicated by the four red dots. Evaluating the patient's glycemic control on those four isolated points suggests the patient is in reasonably good control. However, if we consider the additional data provided by CGM (orange dots), we see that despite routine testing, the patient is missing nocturnal hypoglycemia, and is unaware of post-meal peaks and prolonged daytime hyperglycemia.

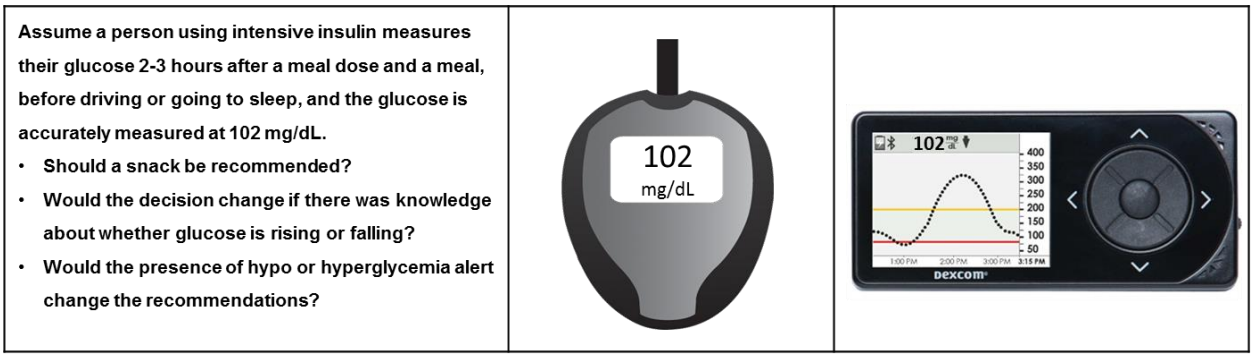
Figure 20: A Patient Checking SMBG 4 x a Day vs Using CGM



The Dexcom G5 Mobile System is a proven tool for enhancing diabetes management and offers patients enhanced decision support beyond the point-in-time measurements of SMBG. The CGM System provides the direction and rate of change in glucose and has alerts and alarms to notify patients when glucose reaches high or low thresholds. Alerts and alarms are particularly useful at night when patients typically do not test using SMBG and for patients that are hypoglycemia unaware and experience reduced warning symptoms prior to a hypoglycemic event.

To further understand the utility of CGM consider the scenario in Figure 21 below, where a patient has tested his glucose with standard SMBG (middle panel), and is about to get in his car and drive. Now contrast this scenario to the information provided with a CGM device (right panel). If the patient's glucose level is 102 mg/dL and dropping, does this change the patient's decision process? In this situation, trend information and alerts are likely more important than the exactness of the number. With the additional information provided by CGM, patients are able to make more informed and timely decisions, improving diabetes management.

Figure 21: An Example of Uncertainty in Diabetes Management Decisions Based On Episodic SMBG



4.2 BENEFITS OF ADJUNCTIVE USE

Although CGM remains a relatively recent clinical development, its impact has been profound. CGM has been shown to improve hypoglycemia detection, prevent hypoglycemic events, and minimize hyperglycemic excursions, while providing immediate feedback on therapeutic decisions persons with diabetes make every day (Pickup et al, 2015). The enhanced decision support provided by CGM, even while using early generation devices, demonstrated that consistent CGM use lowered HbA1c, reduced hypoglycemia and improved quality of life measures (Battelino et al, 2011; Battelino et al, 2012; Frontino et al, 2012; Hommel et al, 2014; Juvenile Diabetes Research Foundation, 2010; O'Connel et al, 2009; Polonsky et al., 2013; Raccah et al, 2009). This finding has been demonstrated in adult and pediatric patients (Battelino et al 2011; Juvenile Diabetes Research Foundation, 2010).

As CGM technology has advanced and experience with the devices has increased, people with T1D have readily incorporated the technology into their diabetes decision making. With increased performance of CGM, how patients use the devices has also evolved, likely related to greater trust in the CGM device (Pettus et al, 2015). CGM alerts are used to detect hypoglycemia and hyperglycemia, and many patients improve their glycemic control by adjusting their insulin therapies based on the rate and direction of change information provided by CGM. The benefits of CGM were demonstrated most recently in the Diamond study (Trial Registration: NCT02282397) presented at the American Diabetes Association Scientific Sessions at an ADA symposium in June, 2016. The randomized controlled study was conducted over 24 weeks and compared adjunctive CGM use of the previous generation Dexcom G4 PLATINUM® with Software 505 (same algorithm used in the Dexcom G5 Mobile System) to usual SMBG management

in 158 adults with T1D using multiple daily insulin injections, aged 26 to 73 years (mean 48+13 years). The main outcome of the study was the between-group difference in HbA1c change at 24 weeks. HbA1c reduction was greater in the CGM group than the usual care group (-1.0+0.8% versus -0.4+0.7%, adjusted difference in mean change of -0.6+0.1%, P<0.001). More participants in the CGM group reduced their HbA1c by >1% HbA1c from baseline (52% versus 19%, odds ratio 5.0, P=0.006) and more reached the HbA1c target of <7.0% (17% versus 4%, odds ratio 6.0, P=0.02). Secondary outcomes of CGM metrics all showed statistically and clinically relevant improvements. CGM-measured time in hypoglycemia below 50 mg/dl, 60 mg/dl, and 70 mg/dl were all reduced from baseline and in comparison to the SMBG group as were CGM-measured time in hyperglycemia above 180 mg/dl and 250 mg/dl and CGM-measured variability. Time in range for CGM was also improved significantly. Similar reductions in HbA1c were obtained across adult age ranges and by people with different education levels and math skills (important for calculating insulin bolus dose).

Interestingly, along with statistical improvements in glycemic control with reduced HbA1c, SMBG frequency decreased more in the CGM group (despite training emphasizing that clinical decisions should be based on a blood glucose measurement) from 5.1 daily measurements (baseline period both groups) to 3.6 in the CGM group and 4.6 in the SMBG group (between group comparison, p<0.001). A post-hoc analysis in the CGM group demonstrated equivalent HbA1c reduction in those participants that averaged a reduction in their SMBG during the study more than one a day, compared to those with an average daily decrease of one or less a day. This is in agreement with other CGM studies that report reduced frequency in SMBG after CGM use (Battelino et al, 2012; New et al, 2015, Chamberlain et al., 2015).

4.3 LIMITATIONS OF CURRENT ADJUNCTIVE LABELING

Despite reported benefits, there are some limitations to the current adjunctive use of CGM. Under the current Indications for Use, the information obtained from the Dexcom G5 Mobile System is not approved for use in diabetes treatment decisions. If episodes of hypoglycemia or hyperglycemia are detected while using the Dexcom G5 Mobile System, patients should confirm the CGM reading with a fingerstick reading before making any treatment decisions, such as drinking orange juice or dosing insulin. The requirement for patients to continue testing using SMBG and confirm CGM readings before treating can result in delayed treatment of diabetes symptoms and perceived low utility of CGM. The current label requiring confirmation by a fingerstick could also undermine confidence in the CGM data for potential prescribers and users.

4.3.1 REDUCED ACCESS AND ADOPTION

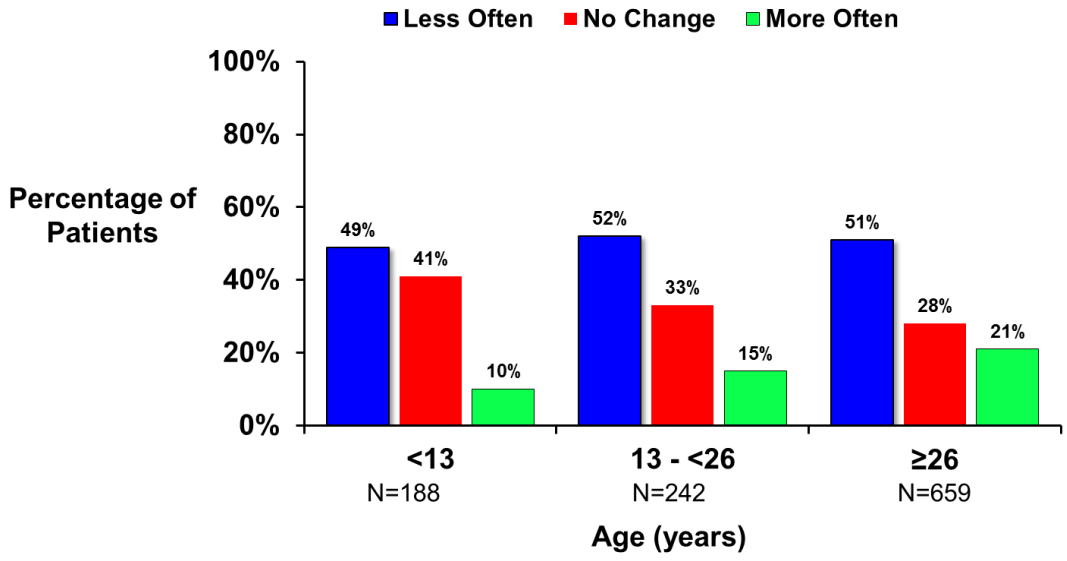
Continuous glucose monitoring technology was first introduced in 1999, and despite over seventeen years on the market, adoption of CGM remains low with only approximately 16% of patients with T1D using it today according to the T1D exchange, a large registry of over 80 clinical practices from leading diabetes centers across the United States. The current adjunctive use and need to confirm CGM readings with

SMBG before making a diabetes management decision is a barrier to use for some patients, prescribers, and payers. Currently, CGM is excluded from Medicare coverage as it is not considered a primary device. The Centers for Medicare and Medicaid Services (CMS) has indicated that CGM does not meet the statutory definition of "durable medical equipment (DME)" because the current labeling requires adjunctive SMBG confirmation prior to dosing or treating. In order for Medicare to consider coverage, a product must first be recognized in a benefit category. For CGM, the benefit category is DME, and to meet the definition of DME, the CGM device would need to serve a primary medical purpose and not be used adjunctively. Thus, CGM would need to meet the statutory definition of DME to become eligible for Medicare coverage.

4.3.2 CURRENT OFF-LABEL USE

For patients currently using CGM, off-label use is not uncommon. Findings from a survey conducted by the T1 Diabetes Exchange (Wong et al, 2014) show that despite the current adjunctive indication, patients wearing CGM commonly reduce their SMBG use after initiating CGM therapies (Figure 22).

Figure 22: Change in Blood Glucose Checks When Wearing a CGM by Age



Wong, J. C., Foster, N. C., Maahs, D. M., Raghinaru, D., Bergenstal, R. M., Ahmann, A. J., & Adi, S. (2014). Realtime continuous glucose monitoring among participants in the T1D Exchange clinic registry. *Diabetes care*, *37*(10), 2702-2709.

A reduction in the frequency of SMBG following continued use of CGM has also been reported in several clinical studies (Battelino et al, 2012; Chamberlain et al., 2015; New et al, 2015). Even with reduced frequency of SMBG, CGM has been shown to improve glycemic and quality of life outcomes. The glycemic improvements with CGM use, despite reduced frequency of SMBG, suggest that some, if not many, diabetes management decisions are based on information obtained from CGM, and these decisions are better informed. As CGM technology improves, this non-adjunctive use of CGM is an increasingly

reported phenomenon despite contradictory labeling. Given current labeling restrictions of the Dexcom G5 Mobile System there are no instructions for patients regarding how and when, and more importantly, when not to use their CGM non-adjunctively.

5 UNMET NEED IN DIABETES

Approximately 1.25 million people in the US have T1D, of which an estimated 208,000 are children under the age of 18 years old (American Diabetes Association, 2014). If patients with T2D requiring treatment with insulin are included, there are between three and four million patients in the US who use insulin daily (Centers for Disease Control and Prevention, 2014). Many of these patients remain in poor glycemic control with elevated HbA1c and problematic hypoglycemia. Hypoglycemia and severe hypoglycemic events may result in confusion, irrational behavior, seizure, loss of consciousness, and death. Annually, approximately 10% of patients and 20% of seniors using insulin experience a loss of consciousness or seizure from hypoglycemia (Cariou et al., 2015, Miller at al., 2015). Many people with TID also experience impaired hypoglycemic awareness which places them at increased risk for severe hypoglycemia, negatively impacting their quality of life (Graveling and Frier, 2010). Additionally, over 70 percent of Type 1 diabetics have HbA1c levels above the recommended target of 7% adults or 7.5% pediatrics (Miller et al, 2015).

Reducing HbA1c achieved with frequent blood glucose monitoring is the primary method of reducing long-term diabetes complications, including, blindness, kidney disease, nerve damage, and vascular disease. This is supported by the Diabetes Control and Complications Trial (DCCT), a large-sample (n=1441), long-term (1983 to 1993), randomized trial of TID in the US and Canada, comparing standard glycemic control to intensive (tight) glycemic control. The study demonstrated overwhelmingly that intensive glycemic control reduced the incidence of eye disease (retinopathy) by 76%, kidney disease (nephropathy) by 50%, and nerve damage (neuropathy) by 60% (The Diabetes Control and Complications Trial Research Group, 1993). Similar results have been observed for patients with T2D that require insulin (Stratton et al, 2000). While this supports the benefit of intensive glycemic control, the DCCT also demonstrated a 3-fold increase in the amount of severe hypoglycemia during intensive therapy, highlighting the limitations of SMBG-based decision making. Hypoglycemia remains a significant limiting factor for intensifying insulin therapy and glucose control, and many patients maintain an inappropriately elevated HbA1c in an effort to avoid hypoglycemia.

Despite almost 100 years of development, insulin dosing remains risky, and when calculating their insulin dose patients must consider a number of factors, including their current or planned activity level, the amount of insulin they have already taken, the accuracy of their last SMBG, and carbohydrate, fat and protein ratios of food they are consuming (Brazeau et al., 2013). Discrepancies between actual and calculated carbohydrates consumed are common, with 67% of meal bolus calculations estimated as incorrect. These miscalculations are often large and negatively impact glucose control resulting in hyper- or hypoglycemia from under or over treatment with insulin (Brazeau et al., 2013). In clinical evaluation reports, even with well-trained patients, dosing mistakes commonly include a discrepancy of up to 20 grams of carbohydrates (30% of the meal consumed), with resulting hypoglycemia or post-meal hyperglycemia (Smart et al., 2012).

5.1 LIMITATIONS OF CURRENT STANDARD OF CARE – SMBG

Although SMBG devices are not indicated to determine insulin doses, they have become the de facto standard used to determine glucose levels and insulin doses. The current guidelines from the American Diabetes Association recommend patients with T1D test 6-10 times per day using SMBG. Frequent SMBG testing is painful and a burden to patients for many reasons, including the inconvenience of testing in public, washing hands, carrying around test equipment, and disposing of bloody waste material.

Despite current ADA recommendations, many patients do not test as often as needed, with over one-third testing three times or less each day (Miller et al, 2015). This reduced testing limits the ability of patients to achieve glycemic goals. Even with frequent routine testing, SMBG point-in-time estimates can be problematic as SMBG provides a single glucose value. Patients do not know the direction and rate glucose is changing over time potentially resulting in inadequate treatment decisions.

One of the most significant problems in diabetes management is a person not recognizing the need to conduct an SMBG when it is clinically valuable to do so. Severe hypoglycemia typically occurs at night or during the day when a person is distracted and unaware that their glucose level is falling or hypoglycemia is imminent (The Diabetes Control and Complications Trial Research Group, 1991). Even with frequent SMBG testing, people with T1D have frequent and protracted hypo- and hyperglycemia (Bode et al, 2005).

The risk associated with intermittent SMBG and nocturnal hypoglycemia is highlighted in a recent paper looking at a pediatric population (ages 2–17 years) (Bachmann, et al. 2016). This study identified nocturnal hypoglycemia (blood glucose < 65 mg/dL) occurring on 32.7% of the nights using masked CGM data; the majority of these events were asymptomatic. The duration of nocturnal hypoglycemia ranged from 10 minutes to more than 600 minutes and of the 128 recorded hypoglycemic events in this trial, only eight were symptomatic and reported by the subjects.

In summary, while the in-home use of blood glucose monitoring devices remains a standard of care, the ability of SMBG to impact hypoglycemia is limited (Brod et al. 2011; Cariou et al, 2015). The limitations associated with SMBG contribute to the small number of people reaching HbA1c target goals and the continued morbidity, mortality and costs associated with hypoglycemia (Klonoff & Reyes, 2013; Prohaska et al., 2012; Naugler et al., 2014).

6 RATIONALE FOR NON-ADJUNCTIVE INDICATION CHANGE

6.1 PROPOSED INDICATION CHANGE AND REGULATORY TIMELINE

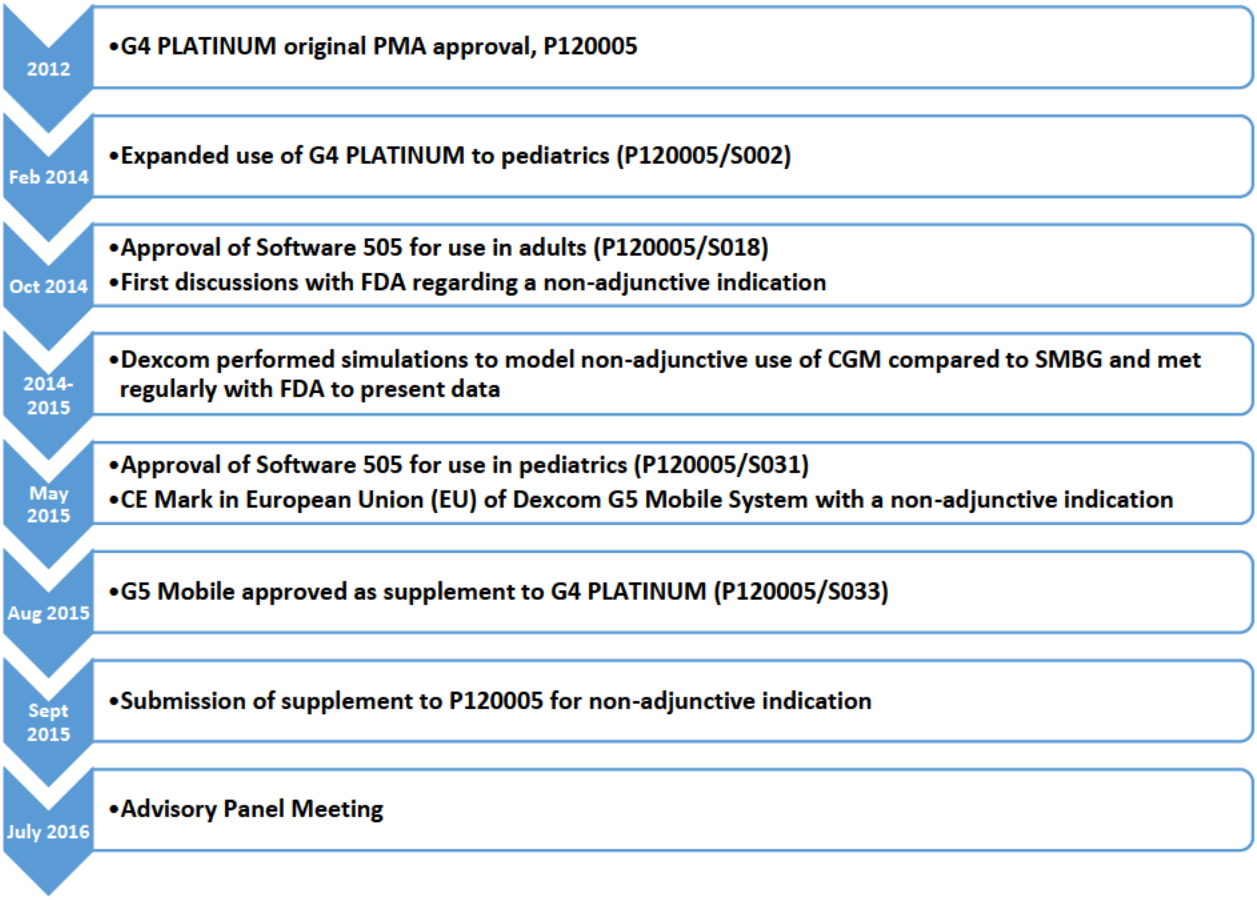
Despite many advances in diabetes management, daily management of diabetes can be problematic with limitations of the current standard of care. CMGs were initially approved by the FDA in 1999. Early devices blinded glucose information to users and limited the CGM use, providing only retrospective data to healthcare professionals. As the technology matured, CGM devices were approved for displaying glucose data to users in real time. Today, CGM technology has advanced significantly with glucose information available on mobile devices and shared remotely with family or friends.

Dexcom received FDA approval for its first real-time CGM System in 2006 for use in adults. Since its first approval, Dexcom's CGM technology has improved significantly. The Dexcom G5 Mobile System is the latest generation in Dexcom's CGM technology. The device is built on the G4 PLATINUM CGM System platform and utilizes Dexcom's newest algorithm technology (Software 505) with a MARD of 9% in adults and 10% in pediatrics. As one of Dexcom's most accurate CGM systems, use of the Dexcom G5 Mobile System has evolved beyond trend information and alerts/alarms. Today, off-label use of the Dexcom G5 Mobile System is an increasingly reported phenomenon with many patients using the information obtained from their CGM to make diabetes treatment decisions, despite contradictory labeling. Currently, the Dexcom G5 Mobile System is only approved for adjunctive use and Dexcom cannot educate patients on how to safely use the device for diabetes treatment decisions. Dexcom recognizes this off-label use as potentially problematic and is taking steps to expand the use of the CGM.

To address off-label use and expand CGM access to patients, Dexcom evaluated the safety and effectiveness of the CGM System with an expanded indication through an evaluation of previous clinical studies and simulated non-adjunctive use. In October 2014, Dexcom began discussing a non-adjunctive indication with the FDA, which would allow CGM information to be used for diabetes treatment decisions. Between 2014 and 2015, Dexcom met regularly with the FDA to present simulation data and to discuss a path for the proposed indication. Dexcom submitted a Premarket Approval Application (PMA) supplement in September 2015 for the proposed indication change. The regulatory timeline is shown in Figure 23 below.

Dexcom's proposed modification to the Indications for Use of the Dexcom G5 Mobile System would allow for non-adjunctive use of the CGM. With this expanded indication, patients would be able to base treatment decisions on information obtained from the Dexcom G5 Mobile System, without performing a confirmatory fingerstick reading. If approved, the Dexcom G5 Mobile System would be the first CGM approved in the United States for non-adjunctive use. This indication would offer people with diabetes an alternative to SMBG for their treatment decisions.

Figure 23: Regulatory Timeline of Non-Adjunctive Indication

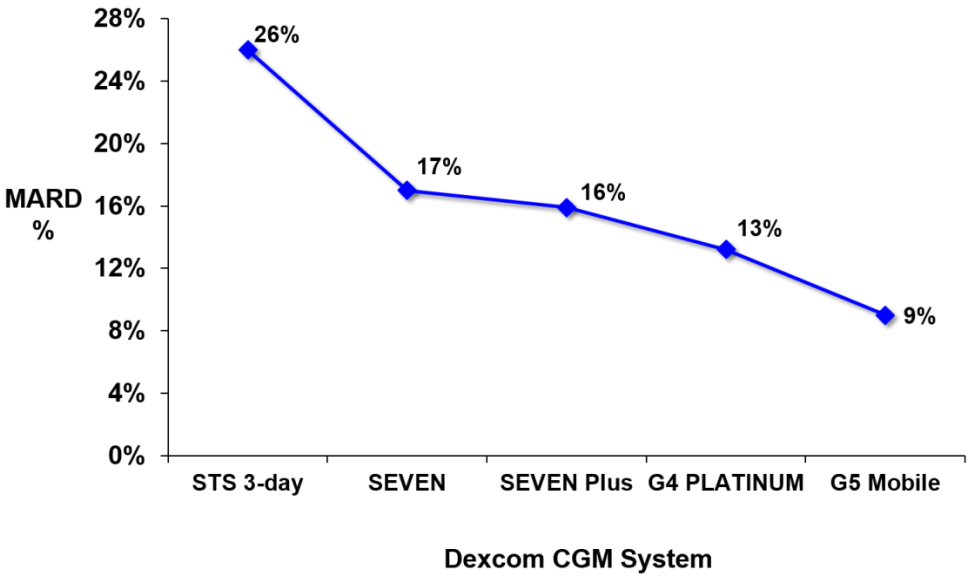


7 SAFETY AND EFFECTIVENESS EVALUATION OF NON-ADJUNCTIVE CGM

7.1 EVOLUTION OF DEXCOM CGM ACCURACY

The commercially available Dexcom G5 Mobile System is Dexcom's most accurate CGM system to date and is the first continuous glucose sensor to be considered by the FDA for non-adjunctive use. CMG accuracy is measured by the MARD from a patient's reference values obtained from blood glucose measurements from a lab analyzer, YSI. YSI measures glucose concentration in plasma samples obtained from venous blood draws while the CGM sensor measures glucose in the interstitial fluid. The MARD indicates the average absolute difference, or distance, between the CGM and YSI values by comparing the YSI blood glucose value to a CGM glucose reading taken immediately after the YSI was collected. The MARD of Dexcom CGMs has steadily decreased from 26% with the first generation STS device in 2006 to 9% in adults (10% in pediatrics) for the Dexcom G5 Mobile System (Figure 24) in 2015.

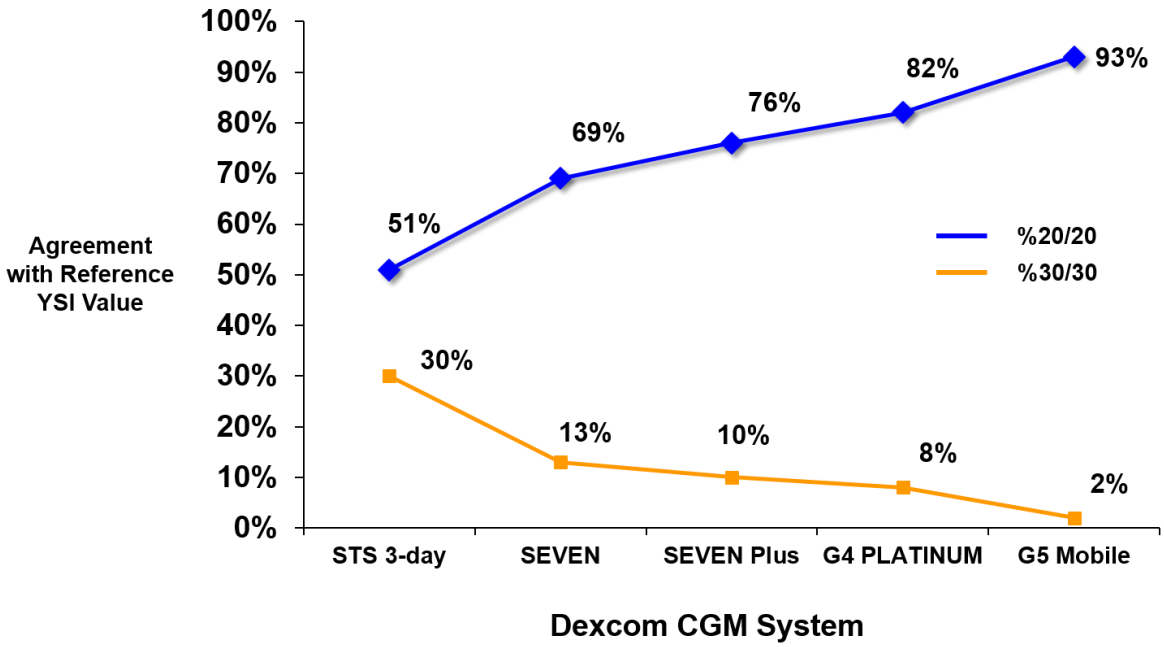
Figure 24: Evolution of Dexcom CGM Accuracy in Adults



Since CGM values that are grossly increased or decreased relative to a reference value would increase risk to a patient using this information to dose insulin, the extent of highly erroneous, or outlying, CGM values is extremely important. A non-adjunctive CGM device would thus need to have an extremely high percentage of point values close to the reference value (within 20%) and an extremely small number of outlier values (>30% compared to a reference YSI value) to ensure that an accurate CGM value was being used for a diabetes treatment decision. The continuous improvement in reducing these outlier values is illustrated graphically in Figure 25 for adults. The agreement of CGM values to YSI values has increased steadily, with 93% of all CGM values less than 20% different than YSI values for the Software 505

algorithm used in the Dexcom G5 Mobile System. As this YSI agreement has increased, the number of outlying CGM values greater than 30% different than YSI has decreased to only 2% of values for the Dexcom G5 Mobile System using Software 505.

Figure 25: Improved Agreement of CGM Values to YSI Values for Adults



This FDA-approved Dexcom G5 Mobile System is the result of over ten years of research and development by Dexcom in CGM technology. Improved accuracy has been achieved through advancements in sensor technology, manufacturing and signal/calibration algorithm management.

A large body of clinical evidence has demonstrated the safety and effectiveness of Dexcom CGMs over the last decade. These studies were submitted to the FDA and provided the foundation for regulatory approval of the CGM systems. Summary results from key clinical studies, shown in Table 19, illustrate the improved performance of Dexcom CGMs. A description of each study is provided below.

Table 19: Summary of Key Dexcom Clinical Studies

Dexcom CGM (population studied)	Year	Total # of Subjects	Matched CGM to YSI Pairs	Mean Absolute Relative Difference	% 20/20[1]	>%30/30[2]
STS 3 day (adults)	2005	91	653	26.2%	50.5%	30.2%
SEVEN (adults)	2006	72	1638	16.6%	69.1%	12.8%
SEVEN Plus (adults)	2008	53	1827	15.9%	76.1%	9.6%
G4 PLATINUM (adults)	2012	72	9093	13.2%	81.7%	7.8%
G4 PLATINUM (pediatrics)	2012	176	2922	17.4%	68.1%	15.4%
G4 PLATINUM with Software 505 (adults)	2014	51	2263	9.0%	93.0%	2.0%
G4 PLATINUM with Software 505 (pediatrics)	2014	79	2262	10.4%	90.6%	3.8%

1 The percentage of CGM values that are within ±20 mg/dL of the paired YSI value at reference levels ≤80 mg/dL or within ±20% at reference levels >80 mg/dL
2 The percentage of CGM values that are greater than ±30 mg/dL of the paired YSI value at reference levels ≤80 mg/dL or greater than ±30% at reference levels >80 mg/dL

STS 3 –day Study in Adults

The purpose of this study was to evaluate the safety and efficacy of the Dexcom Short Term Glucose Sensor (STS) during three days of home use and in the clinic in 91 patients with diabetes mellitus requiring insulin when used as an adjunct to SMBG. The primary endpoint was accuracy as compared to the SMBG meter in a home use setting and the STS met the accuracy endpoint at pre-specified clinical decision levels when compared to the meter. All subjects wore a CGM during the study but were randomized to one of two groups: an active group to gather information on the clinical effectiveness of continuous glucose data, trend information, and alerts when compared to a control group where continuous glucose readings, trend information, and alerts were not provided to the user. All participants wore the continuous glucose Sensor for three, 72-hour periods. A subset of 14 patients underwent YSI testing in the clinic. Safety was characterized by the incidence of Adverse Device Effects. The 19 reported Adverse Events (AE) in 14 subjects consisted of blistering, bullae around the site, edema and erythema. All were mild and required no treatment.

SEVEN

The purpose of this study was to evaluate the safety and effectiveness of the Dexcom STS-7 Continuous Glucose System (STS-7 System) when worn for up to seven days (168 hours) by 72 persons with diabetes mellitus requiring insulin. All participants wore the STS-7 Sensor for one, seven-day wear period (~168 hours). A subset of subjects (28) wore two STS-7 Systems simultaneously during the study. All subjects participated in one, 10-hour in-clinic day on Day 1, 4 or 7 of the study to gain additional accuracy information against a laboratory method (YSI Analyzer) and against the OneTouch Ultra Meter. During the in-clinic day, subjects were asked to have blood draws for evaluation of the YSI blood glucose measurements and blood glucose levels were manipulated per the protocol to ensure that the entire STS-reported glucose range could be evaluated. The efficacy endpoint was accuracy as estimated at clinical levels of 50, 80, 100, 150, and 200 mg/dl compared to a reference YSI value. The efficacy endpoint was met at each decision level. Additionally, precision of the STS-7 System was assessed on those subjects wearing two STS-7 Systems by comparing paired glucose measurements from the two Systems. Safety was assessed by the incidence of device-related adverse events. One subject reported an incident of hypoglycemia requiring assistance during study enrollment. No hospitalization was required.

SEVEN Plus

The SEVEN Plus System contained improvements to the algorithm and receiver user interface, including the addition of trend arrows. The purpose of this study was to evaluate the safety and effectiveness of the SEVEN.2 CGM System (SEVEN Plus) when worn for seven days by 53 adult subjects with diabetes. All subjects wore one sensor for one seven-day period. For the purposes of assessing sensor precision, 18 subjects wore two systems simultaneously: one system was blinded and the other was unblinded (during home use). Performance was evaluated by the proportion of system values within %20/20 of paired YSI values that were collected during three in-clinic sessions on Days 1, 4, and 7 of sensor wear. Safety was assessed by the incidence of device-related adverse events reported. The SEVEN Plus System reported 76% of its glucose readings within %20/20, meeting the pre-specified endpoint. Three non-device related AEs (vasovagal reaction to IV insertion, upper respiratory infection, and nasal congestion treated with acetaminophen) in three subjects were reported.

G4 PLATINUM (adults)

Numerous improvements, including a redesigned sensor and algorithm enhancements, were included in the G4 PLATINUM System. The purpose of this pivotal study was to evaluate the effectiveness and safety of the G4 PLATINUM System when used as an adjunct to blood glucose testing over a seven-day period in 72 adult subjects with diabetes mellitus. All subjects participated in one G4 System sensor session that lasted up to seven days (168 hours). For the purposes of assessing sensor precision, 36 subjects wore two G4 Systems simultaneously: one system was blinded and the other was unblinded (during home use). Subjects participated three in-clinic sessions on Days 1, 4 and 7 of sensor wear. During the in-clinic session, subjects had venous blood draws approximately once every 15 ± 5 minutes and carbohydrate consumption, insulin dosing, and meal timing were manipulated to obtain a wide range

of glucose values. The primary effectiveness endpoint was evaluated by the proportion of system values within %20/20 of paired YSI values and was satisfied because the accuracy of the G4 System in terms of %20/20 was 82%, which was greater than the specified endpoint. Safety was assessed by the incidence of device-related adverse events reported. Thirty-eight AEs were reported. Erythema at insertion site was reported seven times; 12 very slight adhesive erythema AEs and three very slight adhesive edema AEs were recorded. Sixteen other AEs not related to the device were resolved or stable at study termination.

G4 PLATINUM (pediatrics)

The purpose of this study was to evaluate the effectiveness and safety of the G4 PLATINUM System when used as an adjuvant to blood glucose testing over a seven-day period in 176 subjects, 2 to 17 years-old with diabetes mellitus. The subjects participated in one sensor session that lasted up to seven days (168 hours) and wore two sensors simultaneously in either the abdomen, upper buttocks or one at each site. One of the systems was blinded. The subjects between 2-5 years participated in one in-clinic session up to four hours duration on Day 1, 4 or 7, during which they provided at least two fingersticks per hour for measures against SMBG. The subjects between 6-17 years participated in an in-clinic session on Days 1, 4 or 7 up to 6 hours, during which they provided venous blood for evaluation of the System against reference YSI blood glucose measurements. Effectiveness was evaluated by the proportion of system values within %20/20 of paired YSI values. Safety was assessed by the incidence of device-related adverse events reported. Twenty-one AEs in 14 subjects were reported. One AE from pain/discomfort during wear; 16 related to erythema edema and four other/disease/study related. All were resolved by subject study termination.

G4 PLATINUM with Software 505 (adults)

The purpose of this pivotal study was to evaluate the effectiveness and safety of the CGM when used as an adjunctive device to blood glucose testing over a seven-day period in subjects ≥18 years-old with diabetes mellitus. The primary matched paired (CGM-YSI) measurements were collected during one clinic session on Day 1, 4 or 7 of sensor wear. The performance of the system was determined across the seven days of wear time. To collect accuracy information against a laboratory standard (YSI) and against SMBG, subjects participated in one clinic session. Effectiveness was evaluated by the proportion of system values within %20/20 of paired YSI values and was met with 93% of system values within %20/20 of YSI. Safety was assessed by the incidence of device-related adverse events reported. Thirteen AEs were reported. Three very slight erythema were identified at needle insertion areas; nine very slight erythema were identified around adhesive areas. One AE was not related to the device.

G4 PLATINUM with Software 505 (pediatrics)

The purpose of this study was to evaluate the effectiveness and safety of the System with a modified algorithm when used as an adjunctive device to blood glucose testing over a seven-day wear period in pediatric subjects (ages 2 to 17) with diabetes mellitus. Subjects participated in one clinic session during the seven-day wear period which lasted up to four hours for ages 2-5; up to 6 hours for ages 6-12; and up to 12 hours for ages 13-17. School Children (6-12 years old) and Adolescents (13-17 years old) had

laboratory standard (YSI) venous samples collected. The clinic session was interventional for Adolescents only. Blood glucose measurements for 2 to 12-year-old children were observational only (i.e., no glucose manipulation was done). Effectiveness was evaluated by the proportion of system values within %20/20 of paired YSI values and was met with 90.6% of system values within %20/20 of corresponding YSI values. Safety was assessed by the incidence of device-related adverse events reported. Ten AEs (seven erythemas, two edemas, and one vasovagal reaction to IV insertion) in 10 subjects were reported and resolved.

7.1.1 SUMMARY OF SOFTWARE 505 CLINICAL DATA

No additional clinical studies were performed in support of the proposed non-adjunctive indication. However, clinical performance of Dexcom CGM with the Software 505 algorithm, which is used in the Dexcom G5 Mobile System, was evaluated in two separate clinical studies, one with adults and one with pediatrics. A subset of the clinical data used to obtain FDA approval of the Software 505 algorithm in both adults and pediatrics is included below. Additional information regarding these studies is included in the briefing materials.

7.1.1.1 Adult Clinical Study Overview

The Software 505 algorithm was tested in an open label, single arm, multicenter clinical study involving subjects 18 years of age or older with T1D and T2D, using intensive insulin therapy with multiple daily injection or continuous subcutaneous insulin infusion. Fifty-one subjects enrolled in this study at three US sites. Subjects were 46.7 ± 15.8 years old with an age range of 20 to 86 years of age, and approximately half were women. Subjects had diabetes for 24.8 ±14.5, years. 86 percent had type I diabetes, and half were on pumps. Average body mass index was 27, ranged from 20 to 39, and mean HbA1c was 7.8 ±1.1 percent, with a range of 5.8 to 10.9 percent at baseline.

After completing self-training or one-on-one training, and following the instructions-for-use, subjects self-inserted their own sensor in the subcutaneous tissue of their abdomens for seven days of wear. Subjects were instructed to calibrate their receiver twice daily per current recommendations. All subjects used the Bayer Contour Next USB meter for calibrations and for routine blood glucose testing. Subjects were instructed to use CGM information as an adjunct to (and not as a replacement for) standard SMBG guidance of diabetes self-management.

Subjects came to the clinic on day one, four, or seven for a 12-hour session for comparison of CGM readings to both venous and capillary glucose. During their clinic session, subjects had venous draws obtained every 15 minutes for a reference glucose measurement using YSI. The venous samples were arterialized via use of heating pad at the venous sample catheter site to more closely match capillary glucose. Meals, insulin dose amounts, and insulin dose timing were manipulated per a protocol agreed to by the FDA during the clinic session in order to obtain a wide range of glucose values.

At the conclusion of the seven-day wear period, subjects returned to the clinic to remove their sensor and have the insertion sites assessed by study staff, who also documented any adverse device effects that occurred during the study.

7.1.1.2 Pediatric Clinical Study Overview

Similar to the adult study, the pediatric study of the Software 505 algorithm was a one week, open label, single arm, multicenter study and included youth treated with multiple daily injections or insulin pumps. In this study, subjects were 2 to 17 years old and were classified into 3 categories: 1) preschool (ages 2-15), 2) school age (ages 6-12) and 3) adolescents (ages 13-17). There were 79 subjects total (16 in the preschool group, 17 in the school age group and 46 adolescents) that were enrolled from five clinical centers in the United States. Almost all had TID. Mean HbA1c was 8.5± 1.5%. Fifty-seven percent (57%) had previous CGM exposure with 19 percent using it on a routine basis. Self-reported baseline SMBG frequency was 6.7 ±2.3 times a day. Half were female and 60% used pumps.

Subjects wore a single unmasked sensor for the seven-day period. Sensors were self-inserted in the abdomen and/or upper buttocks by the patient or parent after they underwent self-training using a tutorial or one-on-one training by the study staff. Subjects were instructed to calibrate their receiver twice daily per current recommendations.

All subjects participated in one in-clinic session on day one, four, or seven of system wear. Subjects older than 5 years of age underwent intravenous catheterization, allowing glucose samples to be obtained via an arterialized venous sample and measured with a reference YSI every 15 minutes. School aged subjects participated for up to six hours while adolescents were in the clinic for 12 hours. The 6 to 12 year olds did not have glucose purposely manipulated as their study was observational and the subjects managed their diabetes as they normally do. Adolescents underwent purposeful glucose manipulation via protocol guidelines, similar to the adults, in order to achieve glucose levels across the glucose range of sensor performance. All subjects were instructed to use blood glucose measurements for their diabetes management, not CGM readings, during home use, as required per label.

For preschool children aged two to five years old, only capillary samples via fingersticks were obtained every 30 minutes for up to four hours.

CGM was blinded during the clinic session. During home use, CGM data were displayed. However, subjects were instructed to use CGM information as an adjunct to (and not as a replacement for) standard SMBG guidance of diabetes self-management. The study protocol was reviewed by the FDA through the investigational device exemption process and approved by institutional review boards.

7.1.1.3 Summary of Effectiveness Data

Sensor accuracy is a combination of degree of bias, or the degree to which sensor readings are, on average, equal to the reference value, and sensor precision, or the amount of dispersion of readings around the average. Both measures are summarized below. In addition, the accuracy of CGM alerts to

identify both low and high glucose excursions (i.e., hypoglycemic and hyperglycemic events) is summarized, as well as reliability, in terms of the percent of expected sensor readings that are provided.

7.1.1.3.1 AGREEMENT OF CGM READINGS RELATIVE TO YSI

CGM performance was assessed by comparing CGM glucose with immediate temporally prospective matched YSI glucose. Performance statistics included the proportion of CGM values that were within ± 15, 20, 30, and 40 percent of referenced glucose values greater than 80 mg/dL or ± 15, 20, 30, and 40 milligram per deciliter absolute difference at glucose levels less than 80 mg/dL (referred to as % 20/20, %30/30, and %40/40, respectively).The data were further broken down by glucose concentration range (Table 20).

Table 20: System Agreement to YSI within CGM Glucose Ranges

CGM Glucose Range (mg/dL)	Number of paired CGM-YSI readings	Percent within 20 mg/20% YSI	Percent within 30 mg/30% YSI	Percent Greater than 40 mg/40% YSI
ADULTS				
Overall	2263	93%	98%	1%
40-60	120	94%	98%	0%
61-80	226	96%	99%	0%
81-180	738	92%	98%	1%
181-300	798	93%	98%	1%
301-350	229	94%	98%	1%
351-400	152	92%	97%	0%
PEDIATRICS				
Overall	2262	91%	96%	2%
40-60	86	74%	91%	3%
61-80	142	82%	90%	3%
81-180	805	88%	97%	1%
181-300	957	96%	99%	1%
301-350	209	91%	94%	5%
351-400	63	81%	83%	8%

For adult subjects during clinic evaluations, there were 2263 CGM readings that had a corresponding reference YSI, and all of these matched pairs were included in the data analysis. The %20/20 was 93% and the %30/30 was 98%. A total of 2262 CGM readings were matched with reference YSI in the pediatric study, with 91% of CGM values within %20/20 of the reference YSI value.

Table 21 demonstrates consistent accuracy and sensor stability over the 7-day life of the sensor for both the adult and pediatric populations.

Table 21: Sensor Stability Relative to YSI (Accuracy over Time)

Day of Wear	Number of paired CGM-YSI	Mean Absolute Percent Differences	Median Absolute Percent Differences	Percent within 20/20% YSI	Percent within 30/30% YSI	Percent greater than 40/40% YSI
ADULTS						
Day 1	680	10.7%	7.9%	84%	96%	2%
Day 4	777	8.0%	6.4%	96%	99%	0%
Day 7	806	8.5%	7.2%	97%	99%	0%
PEDIATRICS						
Day 1	740	12.7%	8.5%	83%	91%	4%
Day 4	795	8.1%	6.7%	97%	100%	0%
Day 7	727	10.4%	8.4%	91%	98%	1%

7.1.1.3.2 EVALUATION OF SENSOR BIAS RELATIVE TO YSI

CGM accuracy was also assessed by calculating the difference between the CGM reading and the reference YSI value (Table 22). The CGM and YSI values were compared by pairing the CGM reading that fell immediately after the reference values was collected.

The mean percent difference is the average of all positive and negative percent differences between the two devices and demonstrates whether the CGM reads higher or lower than the reference at each glucose range. Another analysis is the absolute percent difference, which provides the percent difference or "distance" between the CGM and YSI values but does not demonstrate whether the CGM is reading, on average, higher or lower than the reference standard. The mean absolute percent difference is the average "distance" (regardless if positive or negative) between CGM readings and YSI values.

Table 22: System Difference to YSI within CGM Glucose Ranges

CGM Glucose Range (mg/dL)	Number of Paired CGM-YSI	Mean Percent Difference	Median Percent Difference	Mean Absolute Percent Difference	Median Absolute Percent Difference
ADULTS					
Overall	2263	2.5%	2.4%	9.0%	7.0%
*40-60	120	-3.3	-2.1	6.9	4.8
*61-80	226	0.8	1.4	6.7	5.4
81-180	738	3.9%	4.1%	9.6%	8.2%
181-300	798	0.6%	0.4%	8.0%	6.1%
301-350	229	4.1%	3.4%	8.0%	5.8%
351-400	152	7.2%	6.3%	9.2%	7.2%
PEDIATRICS					
Overall	2262	1.8%	1.2%	10.4%	7.9%
*40-60	86	-15.3	-13.2	16.1	13.2
*61-80	142	-4.8	-1.0	11.8	7.7
81-180	805	1.9%	0.7%	10.6%	8.1%
181-300	957	2.2%	1.0%	8.1%	6.5%
301-350	209	7.8%	6.5%	11.0%	7.9%
351-400	63	14.9%	11.6%	15.2%	11.6%

*For CGM≤ 80 mg/dL, the differences in md/dL are included instead of percent differences (%).

The accuracy measures for the adult population were based upon 2263 paired glucose results and demonstrated a 9.0% MARD whereas the pediatric population had a 10.4% MARD from 2262 CGM values paired to YSI values.

Analysis of Outliers

For adults, there were 33 data points (out of 1738 matched pairs) that were more than 30% discrepant from the YSI reference at glucose >100 mg/dl. Thirty-two of these had a high bias (>30%) and could lead to an increased correction dose, increasing the risk of hypoglycemia. Of these, 18 occurred on the first half of Day 1, 9 occurred on the second half of Day 1, and only 5 occurred after Day 1.

In the pediatric study, there were 59 data points (out of 1896 matched pairs) that were more than 30% discrepant from the YSI reference at glucose >100 mg/dl. Forty-eight of these had a high bias (>30%) and could lead to an increased correction dose, increasing the risk of hypoglycemia. Of these, 28 occurred on the first half of Day 1, 16 occurred on the second half of Day 1, and only four occurred after Day 1.

7.1.1.3.3 ACCURACY OF ALERTS AND ALARMS

The Dexcom G5 Mobile System has programmable High and Low Glucose Alerts that can be changed by the user and a non-changeable Low Glucose Alarm set at 55 mg/dL. The user is instructed to consult with their physician to determine appropriate alert settings.

To assess the ability of the system to detect high and low glucose levels, the CGM results were compared to YSI results at low and high blood glucose levels and it was determined if the alert may have sounded.

Low Glucose Alert

Estimates of how well the adjustable Low Glucose Alert performed within 15 minutes of the reference reading are presented in Table 23. The True Alert Rate is the percent of time the device alarmed when the reference blood glucose level was at or below the alert setting within 15 minutes before or after the device alarmed. The Hypoglycemia Detection Rate shows the percent of time the reference blood glucose level was at or below the alert setting and the device alarmed within 15 minutes before or after the blood glucose was at or below the alert settings. The true alert rate for the default alert setting of 80 mg/dL was 95% for adults and 86% for pediatrics.

When the threshold low glucose alert was set at the default alert setting of 80 mg/dl for adults, the CGM system detected true hypoglycemia (the YSI glucose measurement was less than 80 mg/dl) 90% of the time within 15 minutes and alerted correctly 95% of the time within a 15-minute window, meaning there was a 5% false alert rate. Similarly, for pediatrics, true hypoglycemia was detected 91% of the time and the alert was correct 86% of the time when the low alert was set to 80 md/dL.

Table 23: Hypoglycemic Alert Evaluation

Hypoglycemic Alert Level (mg/dL)	True Alert Rate	False Alert Rate	Hypoglycemia Detection Rate	Hypoglycemia Missed Detection Rate
ADULTS				
55	71%	29%	68%	32%
60	85%	15%	83%	17%
70	92%	8%	91%	9%
80	95%	5%	90%	10%
90	96%	4%	94%	6%
PEDIATRICS				
55	22%	78%	75%	25%
60	42%	58%	78%	23%
70	68%	32%	75%	25%
80	86%	14%	91%	9%
90	90%	10%	93%	7%

High Glucose Alert

Estimates of how well the adjustable High Glucose Alert performed within 15 minutes of the reference reading are presented in Table 24. The True Alert Rate is the percent of time the device alarmed when the reference blood glucose level was at or above the alert setting within 15 minutes before or after the device alarmed. The Hyperglycemia Detection Rate shows the percent of time the reference blood glucose level was at or above the alert setting and the device alarmed within 15 minutes before or after the blood glucose was at or above the alert settings.

When the high threshold alert was set at the default alert setting of 200 mg/dl for adults, the CGM detected true hyperglycemia (YSI glucose greater than 200 mg/dl) 98% of the time within 15 minutes and alerted correctly 96% of the time. Similarly, true hyperglycemia was detected 97% of the time for pediatrics and the alert was correct 94% of the time for pediatrics when the high alert was set to 200 mg/dL.

Table 24: Hyperglycemic Alert Evaluation

Hyperglycemic Alert Level (mg/dL)	True Alert Rate	False Alert Rate	Hyperglycemia Detection Rate	Hyperglycemia Missed Detection Rate
ADULTS				
120	98%	2%	100%	0%
140	97%	3%	99%	1%
180	97%	3%	99%	1%
200	96%	4%	98%	2%
220	94%	6%	98%	2%
240	93%	7%	95%	5%
300	86%	14%	90%	10%
PEDIATRICS				
120	98%	2%	99%	1%
140	97%	3%	98%	2%
180	94%	6%	98%	2%
200	94%	6%	97%	3%
220	93%	7%	96%	4%
240	88%	12%	94%	6%
300	69%	31%	84%	16%

7.1.1.3.4 NUMBER OF READINGS PROVIDED

The system is capable of providing a reading up to every 5 minutes, or up to 288 readings per day. For a variety of reasons, the system may not display a glucose reading and readings are missed. Table 25 shows the average number of readings provided per sensor wear day.

Table 25: Mean Number of System Readings within Wear Days

Population	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	All Days
Adult	98%	99%	98%	98%	96%	99%	97%	98%
Pediatric	96%	96%	95%	96%	93%	95%	93%	95%

7.2 PREMARKET CLINICAL STUDY

The Dexcom G5 Mobile System is commercially available and the safety and effectiveness of current use has been established through clinical studies and post-market surveillance. Assessing the risk of non-adjunctive use of the Dexcom G5 Mobile System required an evaluation of severe hypoglycemic events, which can be a rare event in clinical trials. Further, getting a clear separation of non-adjunctive and adjunctive use cohorts is not feasible as CGM users still calibrate with BG results. Instead of performing a premarket clinical study to support expanded use, Dexcom and the FDA agreed that a simulation approach would provide a superior means to evaluate CGM-based treatment decisions because severe hypoglycemia can be modeled directly, without exposing patients to any risks of these events. The simulation data, described in the section below provides reasonable assurance of safety and effectiveness for non-adjunctive use of the Dexcom G5 Mobile System and Dexcom proposes to confirm safety in the post-market setting.

7.3 COMPUTER SIMULATIONS

7.3.1 RATIONALE FOR USE OF COMPUTER SIMULATIONS

Controlled clinical studies do not fully represent the true benefit-risk profile of a device when it is used in a real-world setting and may not fully assess uncommon and high risk events, such as severe hypoglycemia. Thus, some regulatory bodies, including the FDA, are now considering a role for computer modeling and simulation to help assess the safety and/or effectiveness of the product prior to approval. In January 2014 FDA produced a draft guidance titled “Reporting of Computational Modeling Studies in Medical Device Submissions.” In parallel, FDA contributed to the establishment of an ASME Standardization Committee V&V-40 “Verification and validation in computational modeling of medical devices.”

The growing acceptance of simulations is driven by advancements in the simulation of complex physiological processes made possible by significant research investments over the last 10 years in the area of physiological modeling. Large scale research initiatives, such as the Virtual Physiological Human funded by the European Commission or the portfolio of grants coordinated through the USA Interagency Modeling and Analysis Group, have driven robust development of *in silico* technologies, in particular those capable of modeling individual subjects.

In Silico Clinical Trials (ISCT) are defined as "the use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention" (Viceconti et al, 2016). These simulations recreate the concept of an *in vivo* trial using an *in silico* approach, where a large number of individual patients is modeled by initializing a disease/intervention model with quantitative information either measured on an individual (subject-specific model) or inferred from population distributions of those values (population-specific model).

An essential requirement to perform large scale ISCT is the *availability of an individualized model* of a patient's physiological response to the drug- or medical device-based treatment under test that accounts for *inter-individual variability* and is able to describe a large number of individual virtual subjects (VS). Another important benefit of ISCT is the possibility to test *high risk situations* related to the occurrence of rare events, which would not be observable in an *in vivo* clinical trial because of their limited size, duration, and difficulty in recruitment. Therefore, ISCT are uniquely suited to define the limits and robustness of treatments based on medical devices without exposing human patients to risks.

In addition, ISCT allow *running multiple tests on the same virtual patient*, resulting in answers to the following "what if" questions. What if patient A uses a treatment based on device C instead of device B when the same surrounding conditions are maintained? What if patient A uses a treatment based on device C with settings D instead of settings E when the same surrounding conditions are maintained? What if patient A uses a treatment based on device C with performance F instead of performance G when the same surrounding conditions are maintained? Clearly, these questions cannot be answered by *in vivo* clinical trials because the same surrounding conditions, including a patient's physiology and behaviors, cannot be exactly repeated in real-life. *In silico* clinical trials are thus powerful investigation tools and Dexcom utilized this technology to assess non-adjunctive use of the Dexcom G5 Mobile System.

To provide a more thorough assessment of benefits and risks of non-adjunctive CGM use than could be obtained with a clinical study, Dexcom performed two distinct simulations. The first simulation was a two-week simulated clinical study that compared glycemic outcomes (time in range, time in hyperglycemia, time in hypoglycemia, and average rate and average duration of events below 70 mg/dL or 50 mg/dL) from CGM and SMBG-based treatment decisions. This simulation was conducted in collaboration with the University of Padova. Based on literature data, Dexcom clinical studies and field data, and common clinical practice, a model of SMBG-based or CGM-based decision making intended to reflect real-life patient behavior was constructed. The ISCT allowed a direct comparison of the benefit-risk profile of CGM-based decision making versus SMBG-based decision making over multiple meals over multiple days in a large number of virtual subjects with diverse behaviors. This simulation was intended to assess the overall risk of CGM-based dosing decisions compared to SMBG.

The second simulation utilized a simplistic model for single meal-time dosing and was intended to identify specific situations that could result in high risk with non-adjunctive CGM use. This simulation model allowed for individual manipulation of physiological and situational parameters providing a rapid evaluation of the impact of each parameter on risk of hypoglycemia and hyperglycemia. This simulation

compared the glycemic consequences of meal-time insulin dosing using glucose data from CGM or SMBG. The combination of both the two-week simulation and meal-time dosing simulation provide a direct comparison between CGM and SMBG when used for diabetes decision-making and also identified specific situations that elevated risk for CGM-based treatment decisions.

7.3.2 TWO-WEEK SIMULATION STUDY

The two-week simulation study was performed in collaboration with the University of Padova (Italy) using a T1 Diabetes Decision Making Model. This study evaluated safety and effectiveness of non-adjunctive use of the Dexcom G5 Mobile System compared to SMBG. An overview of this simulation study is provided in Table 26.

Table 26: Overview of Two-Week Simulation Study

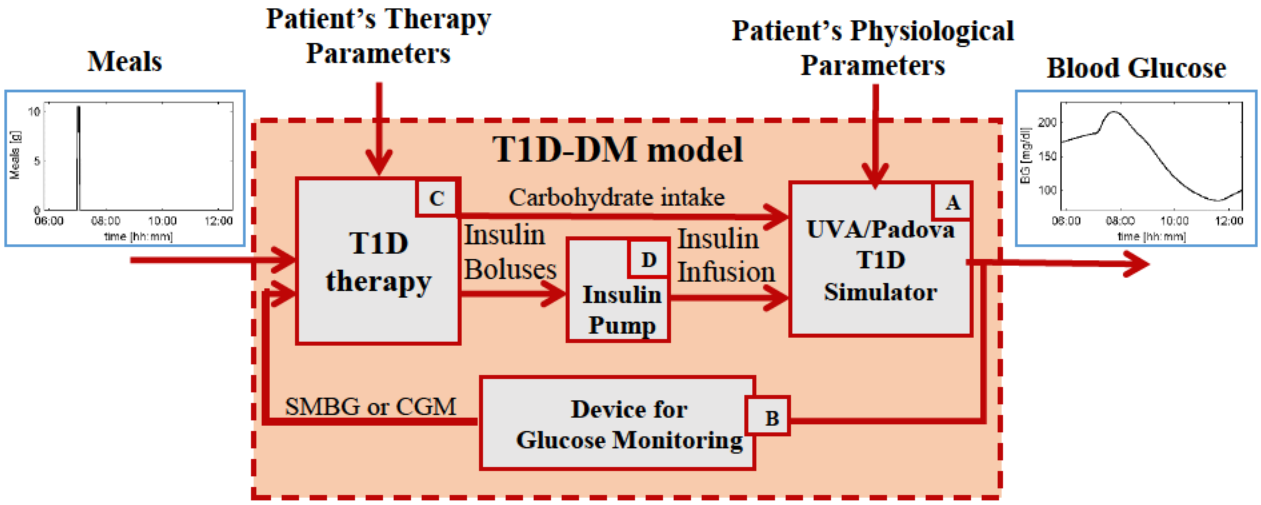
Study Duration	14 days (2 seven day CGM sessions)
Population	200 total (100 adult virtual subjects and 100 pediatric virtual subjects)
Behaviors	100 different randomizations of behavioral parameters were modeled for each virtual subject
Hypoawareness Groups	2 groups were simulated 1. Mixed hypoawareness: 80% normal awareness, 20% impaired awareness 2. Impaired hypoawareness: 100% impaired awareness
Outcome Metrics	1. Time in severe hypoglycemia (below 50 mg/dL) 2. Time in hypoglycemia (below 70 mg/dL) 3. Time in target glucose range (between 70 mg/dL and 180 mg/dL) 4. Time in hyperglycemia (above 180 mg/dL) 5. Time in severe hyperglycemia (above 250 mg/dL) 6. Average rate and average duration of events below 70 mg/dL and 50 mg/dL

7.3.2.1 Description of the T1D-DM Model

The T1D Decision Making Model (T1D-DM Model) used in this simulation study is illustrated in Figure 26 and consists of four main components:

1. UVA/Padova T1D Simulator
2. Glucose monitoring model (SMBG or CGM)
3. T1D therapy model
4. Insulin pump model

Figure 26: T1D Decision Making Model



1. UVA/Padova T1D Simulator (Block A in Figure 26)

The UVA/Padova T1D Simulator is a validated large-scale maximal computer model of glucose, insulin and glucagon dynamics in T1D patients jointly developed by the University of Virginia (Charlottesville, Virginia) and the University of Padova (Padova, Italy). The simulator was accepted by the FDA in 2008 as a substitute to animal trials for the preclinical testing of certain insulin treatments. This simulator has been used by 32 research groups in academia and 5 companies, leading to more than 63 publications in peer-reviewed journals. The simulator has been adopted by the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Consortium to test control algorithms and accelerate closed-loop studies, with a number of Investigational Device Exemption approvals achieved solely on simulations.

The model was initially derived from 204 actual nondiabetic individuals and later modified to account for the glucose-insulin dynamics found in people with T1D. The simulator has been updated in 2013 (Dalla Man *et al.*, 2014), including an improved model of the glucose kinetics in hypoglycemia and models of glucagon kinetics, secretion and action. The updated simulator was validated using T1D data sets (Visentin *et al.*, 2014). In 2015 (Visentin *et al.*, 2015), a circadian model of insulin sensitivity was also incorporated, thus extending its validity from simulation of a single meal to simulation of multiple days. A total of 100 virtual adult and 100 virtual pediatric subjects were created to cover the range of physiological parameters expected in the T1D population. Each virtual subject is described by a set of physiological parameters describing glucose gastro-intestinal absorption, endogenous production and utilization, insulin subcutaneous absorption, action and degradation, and glucagon secretion, action and

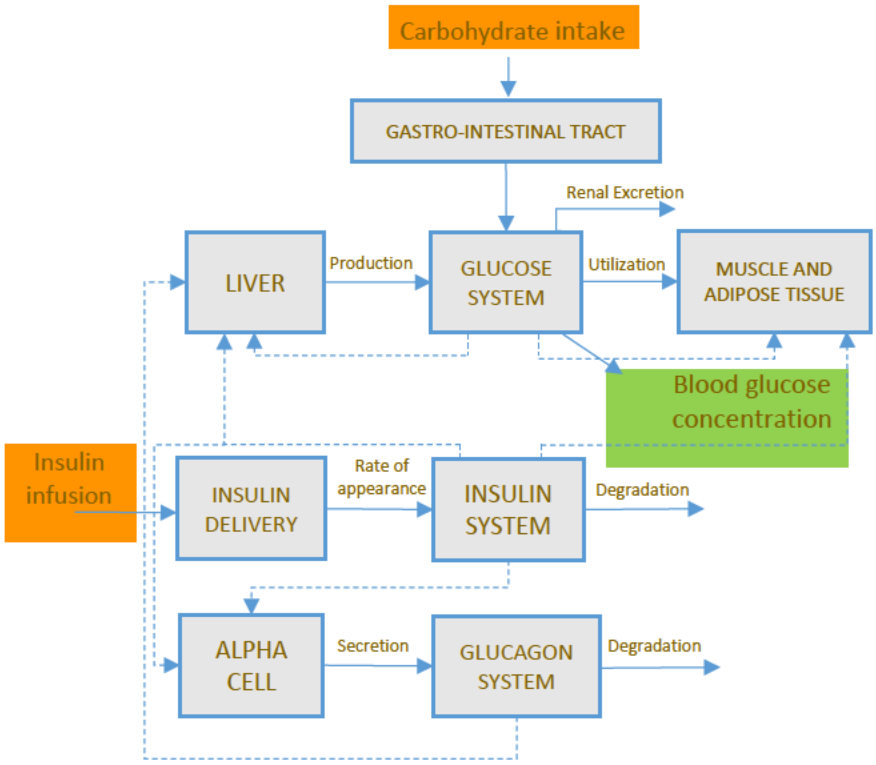
degradation. Metabolic characteristics of adult and pediatric virtual subjects validated for use in the simulator are listed in Table 27.

Table 27: Key Demographics and Metabolic Characteristics of Virtual Subjects

	Adult virtual subjects			Pediatric virtual subjects		
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**
Age (years)	32.3 (9.6)	20	65	6.1 (3.4)	1	12
Body Weight (kg)	69.7 (12.4)	46.7	106.1	30.0 (4.6)	21.0	41.7
T1D duration (years)	10.9 (9.9)	1	57	3.5 (2.6)	1	10
Insulin to carb ratio (g/U)	15.9 (5.3)	7.2	29.5	23.6 (6.6)	8.0	33.7
Insulin sensitivity factor (mg/dl/U)	43.2 (9.9)	26.2	67.1	110.2 (21.2)	56.7	172.1
Fasting plasma glucose (mg/dl)	119.6 (6.7)	107.5	137.8	119.8 (6.4)	104.7	134.3
Basal insulin (U/hour)	1.2 (0.3)	0.6	2.1	0.4 (0.1)	0.2	0.7

As illustrated in Figure 27, the UVA/Padova T1D simulator receives the virtual subject's carbohydrate intake (g/min) and insulin infusion (units of rapid acting insulin [IU]/min) as inputs (shaded orange in the figure) and outputs the subject's resulting glucose concentration in mg/dL (shaded green in the figure).

Figure 27: Overview of UVA/Padova T1D Simulator



2. Glucose monitoring model (SMBG or CGM, Block B in Figure 26)

This model simulates either SMBG measurements or CGM outputs, including CGM glucose trace, trend arrows, high/low glucose alerts and low glucose alarms, based on simulated blood and interstitial glucose provided by the simulator. In the CGM model, glucose readings are generated by applying error models that include the major sources of CGM inaccuracy, such as systematic biases due to imperfect calibration and measurement noise. CGM model parameters were derived from Dexcom's four clinical datasets (two in adults and two in pediatrics) used for the approval of the Software 505 algorithm. In these studies, blood glucose reference samples were collected and measured by a laboratory standard YSI analyzer during Days 1, 4 and 7 of CGM wear. SMBG errors were simulated using a model of the statistical distribution of the SMBG measurement error, derived from temporally matched meter and YSI measurements in the adult clinical dataset also obtained from clinical studies to support the Software 505 algorithm. Further details on methodology used to develop the CGM and SMBG models from clinical data can be found in Facchinetti et al., 2015, Vettoretti et al., 2015, and Vettoretti et al., 2016.

3. T1D Therapy Model (Block C in Figure 26)

The T1D therapy model simulates the patient behavior of administering insulin or consuming carbohydrates based on SMBG or CGM glucose values. The therapy model inputs are meal information, glucose information from SMBG or CGM, and individual subject therapy parameters. The outputs are carbohydrate intake and insulin boluses. The therapy model also uses hypoglycemic symptoms to trigger treatments.

Figure 28: SMBG-Driven T1D Therapy Model

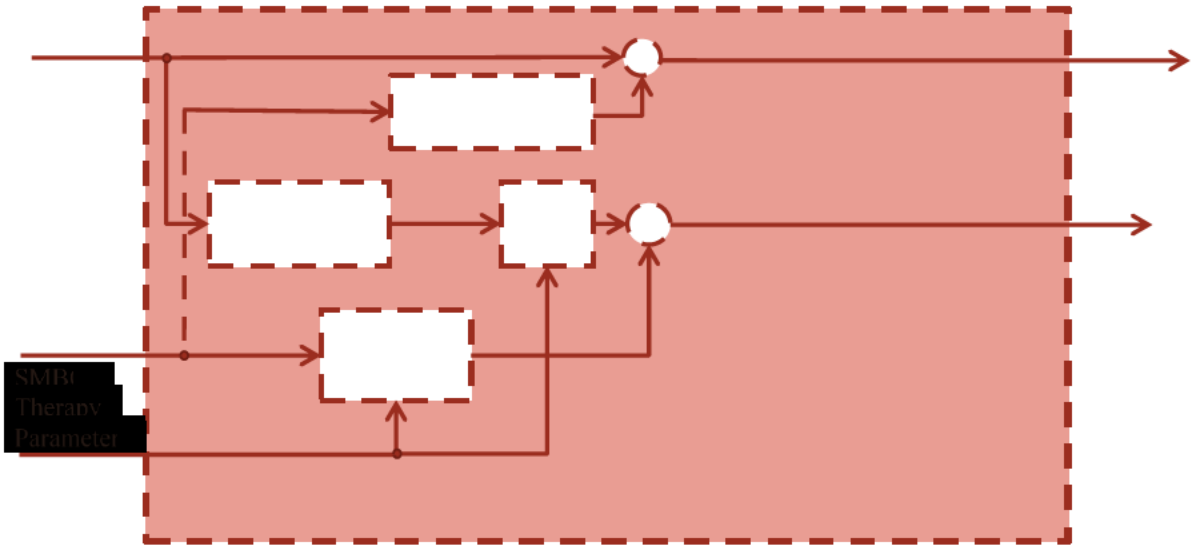


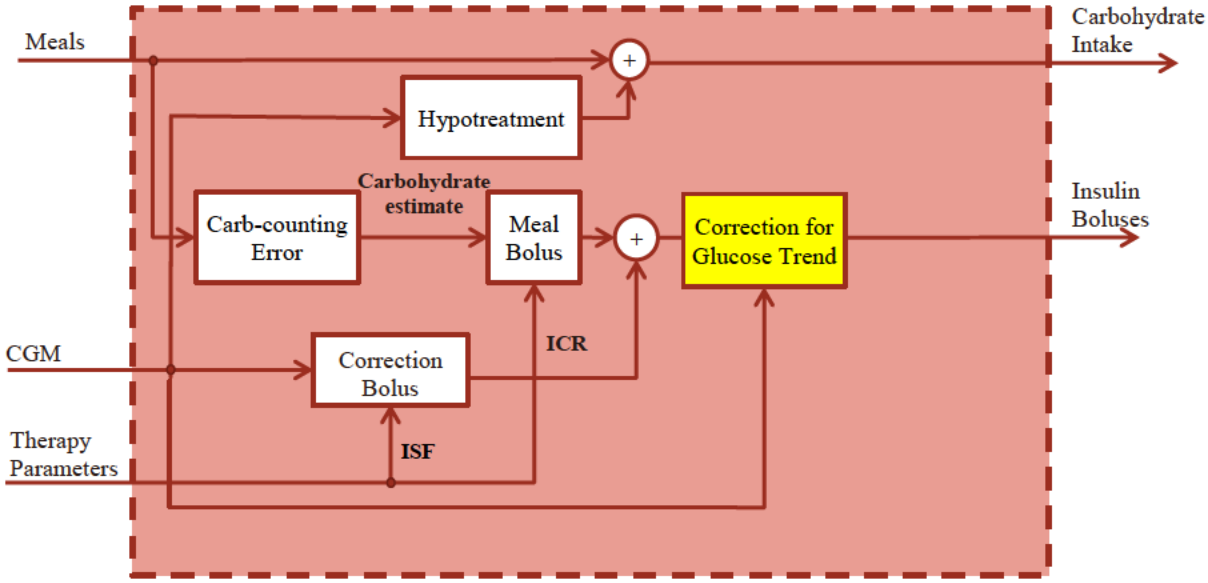
Figure 28 details the SMBG-driven T1D therapy model. SMBG-based diabetes management was simulated as follows:

- Treatments for hypoglycemia were provided when the patient recognized hypoglycemic symptoms (i.e. blood glucose concentration dropped below the assumed threshold of hypoglycemia awareness) and low glucose was confirmed by SMBG or when routine (post-meal and pre-sleep) SMBG measurements revealed low glucose.
- Pre-meal insulin boluses were calculated based on the patient's estimate of meal carbohydrate content (with carbohydrate counting errors included) and then corrected to a target glucose level according to the simulated SMBG measurement.
- Insulin correction boluses were generated and calculated according to the SMBG measurement to correct hyperglycemia after meals in a subset of subjects that were simulated to test their post-meal BG concentration with SMBG and before sleep for all subjects.

The insulin dose was based upon the standard dosing equation seen below:

$$dose = \frac{estimated\ glucose - target\ glucose}{insulin\ sensitivity\ factor} + \frac{estimated\ carbohydrates}{insulin\ to\ carbohydrate\ ratio}$$

Figure 29: CGM-driven T1D Therapy Model



The CGM-driven T1D therapy model (Figure 29) is similar to the SMBG model, except that it includes a correction based upon the glucose trend arrow (highlighted in yellow in the figure).

CGM-based diabetes management was simulated as follows:

- Treatments for hypoglycemia were generated in response to CGM low glucose alerts or alarms, in response to routine (post-meal and pre-sleep) checks that revealed low glucose, or in response to hypoglycemic symptoms (i.e. when blood glucose concentration falls below the patient's threshold of hypoglycemia awareness and low glucose is confirmed with CGM, or if CGM is discordant with symptoms, but SMBG confirms that blood glucose is low).
- Pre-meal insulin boluses were calculated based on the patient's estimate of meal carbohydrate content and then corrected to a target glucose according to the simulated CGM glucose reading and trend arrow.
- Correction boluses were generated in response to CGM high glucose alerts and CGM checks after meals and before sleep that revealed high glucose and calculated according to CGM glucose reading and trend arrow.

The insulin dose calculation was based on the standard dosing equation plus adjustments for CGM trend arrows (Scheiner, 2015). These trend adjustments were made as follows:

- ≥ 2 mg/dL/min trend arrow (1 or 2 up arrows): Add 50 mg/dL to estimated glucose
- + 1-2 mg/dL/min trend arrow (45 degree up arrow): Add 25 mg/dL to estimated glucose
- +1 to -1 mg/dL/min: No adjustment to estimated glucose
- -1 to -2 mg/dL/min trend arrow (45 degree down arrow): Subtract 25 mg/dL from estimated glucose
- ≤ - 2 mg/dL/min trend arrow (1 or 2 down arrows): Subtract 50 mg/dL from estimated glucose

4. Insulin pump model (Block D in Figure 26)
   The insulin pump was used as the device model for continuous-time infusion of rapid-acting insulin in the subcutaneous insulin. The total infusion was defined as the sum of the bolus infusion plus the constant basal infusion. The bolus administration was an impulsive administration of insulin as calculated by the T1D therapy model whereas the basal administration was a constant infusion rate (basal = 0.47 x total daily insulin) as determined by a guideline by Davidson et al (Endocrine Practice, 2008).

7.3.2.2 Process for Two-week Simulation Study

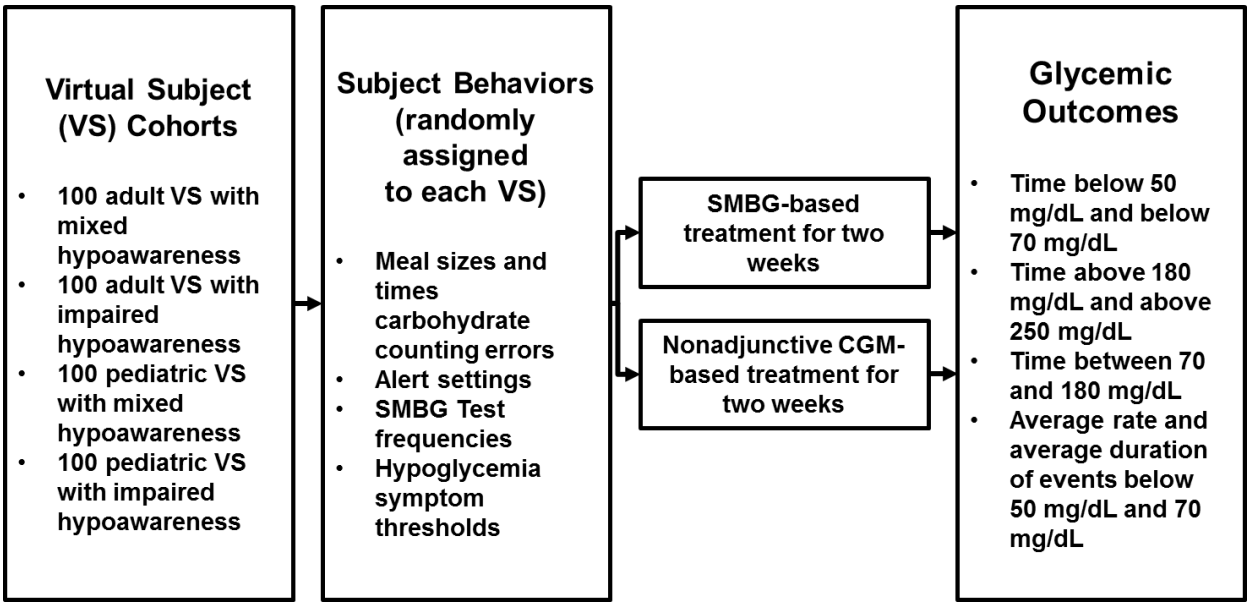
Using the T1D decision making model described above, simulations were run in a total of 200 virtual subjects with unique physiologies over a simulated two-week period, reflecting a total of two CGM wear sessions. These subjects were characterized by a mixture of hypoglycemia awareness and subject behaviors (Figure 30) to more comprehensively assess the risks and benefits of CGM-based decision making versus SMBG-based decision making.

Patients with hypoglycemia unawareness are at a higher risk of severe hypoglycemia from insulin-dosing because characteristic symptoms of hypoglycemia (such as palpitations, sweating and anxiety) are not readily recognized at normal low glucose levels. In order to assess risk in this population, the simulation was performed twice assuming the virtual subjects belong to two groups of hypoawareness, one in which all subjects experiencing impaired hypoawareness and one in which hypoglycemia unawareness was varied, or mixed. Since Olsen et al. (2014) report that about 20% of general population has impaired hypoglycemia awareness, the mixed hypoawareness group consisted of 80% of subjects with normal hypoawareness and 20% with impaired hypoawareness. In the simulator, normal awareness was associated with symptom recognition at a glucose threshold between 55 mg/dL and 70 mg/dL, while symptom recognition for impaired awareness was assumed to occur at a threshold between 40 mg/dL and 55 mg/dL.

Within each cohort, each of the 100 virtual adult subjects and 100 virtual pediatric subjects comprising the UVA/Padova T1D Simulator were duplicated in each hypoglycemia awareness group, resulting in a total of 4 cohorts studied:

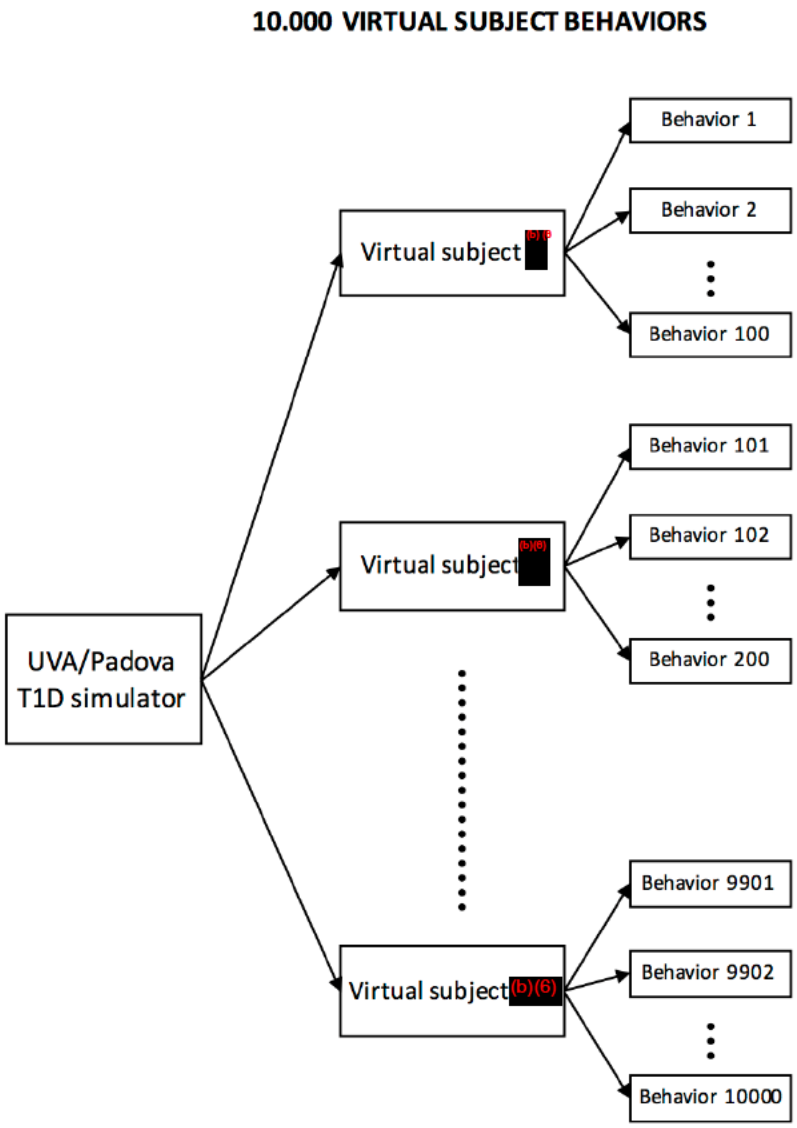
- 100 virtual adult subjects with mixed hypoawareness
- 100 virtual adult subjects with impaired hypoawareness
- 100 virtual pediatric subjects with mixed hypoawareness
- 100 virtual pediatric subjects with impaired hypoawareness

Figure 30: Two-week Simulation Process



In addition, each subject within these four cohorts of virtual subjects was also modeled with 100 different behaviors (i.e., meal timing, meal sizes, alert settings, carbohydrate counting errors, SMBG test frequencies, and subject-specific symptom thresholds) resulting in a total of 40,000 combinations of simulated physiologies and user behaviors (Figure 31).

Figure 31: Generation of 10,000 Virtual Subject Behavior Combinations for One Virtual Subject Cohort



Three meals per day with a range of carbohydrate content were randomly generated for each subject assuming a uniform distribution of meal time between 6:30 AM and 8:00 AM for breakfast, 11:30 AM and 1:00 PM for lunch, and 6:30 PM and 8:00 PM for dinner.

Finally, CGM high and low glucose alert thresholds were varied across subjects and based upon actual use of the Dexcom CGM system. In each virtual subject, the low alert threshold was randomly set to 80, 70 or 55 mg/dl and the high glucose alert settings were randomly assigned to 180, 200, 250, 300, 350 and 400 mg/dL. High and low glucose alert thresholds were held constant across the two-week period.

The Dexcom G5 Mobile System requires that the sensor be replaced after seven days of use; therefore, two sensors, each lasting seven days, were simulated per subject. Additionally, CGM sensor calibrations were assumed to occur at 6:00 AM and 6:00 PM.

Two simulations were run for each virtual subject (with the same physiologies and subject behaviors): one where SMBG was used for diabetes treatment decisions and one where CGM was used for diabetes treatment decisions. This clear separation between non-adjunctive CGM use and SMBG-based decisions allowed Dexcom to compare decisions based on CGM data with decisions based on SMBG measurements simultaneously on the same virtual patient in parallel, eliminating potential behavioral changes and or physiological differences that could occur between cohorts or over time in clinical studies. Each virtual subject acted as his own control.

To compare the impact of CGM-based treatment decisions versus SMBG-based decisions, we assessed, for each combination of virtual subject and behavior, the following glycemic outcomes used as common endpoints in diabetes trials (Battelino et al, 2012; Juvenile Diabetes Research Foundation, 2010):

1. Time in severe hypoglycemia (below 50 mg/dL)
2. Time in hypoglycemia (below 70 mg/dL)
3. Time in target glucose range (between 70 mg/dL and 180 mg/dL)
4. Time in hyperglycemia (above 180 mg/dL)
5. Time in severe hyperglycemia (above 250 mg/dL)
6. Average rate and average duration of events below 70 mg/dL and 50 mg/dL

To illustrate how the simulator works, a sample day for one virtual subject is described. The simulated blood glucose, CGM readings, carbohydrate intake and insulin boluses are shown in Figure 32. The figure below depicts the simulated blood glucose (black trace), CGM readings at 5 minute intervals (black dots), basal and bolus insulin doses (blue red line and red spikes), true carbohydrate intake (green circles) and estimates of meal carbohydrate content (blue squares).

This virtual subject had the following physiology and behavioral parameters:

- Age: 25
- Gender: female
- Hypoawareness: impaired (symptom threshold = 51 mg/dL)
- Physiology: insulin sensitivity factor of 55 mg/dL/U, insulin to carb ratio of 15 grams/U
- Meal times: Breakfast – 7:34 AM, lunch – 11:41 AM, dinner – 6:43 PM
- Meal sizes: Breakfast – 40 grams, lunch – 100 grams, dinner – 99 grams
- Carbohydrate estimates: Breakfast – 46 grams, lunch – 88 grams, dinner – 137 grams
- CGM alerts: 70 mg/dL low alert, 200 mg/dL high alert

The virtual subject wakes up at 6:00 AM with a blood glucose of 132 mg/dL. She eats breakfast at 7:34 AM and estimates that her breakfast contains 46 grams of carbs (actual amount was 40 grams). When she calculates her breakfast insulin bolus, her CGM reads 149 mg/dL, slightly above her actual blood glucose

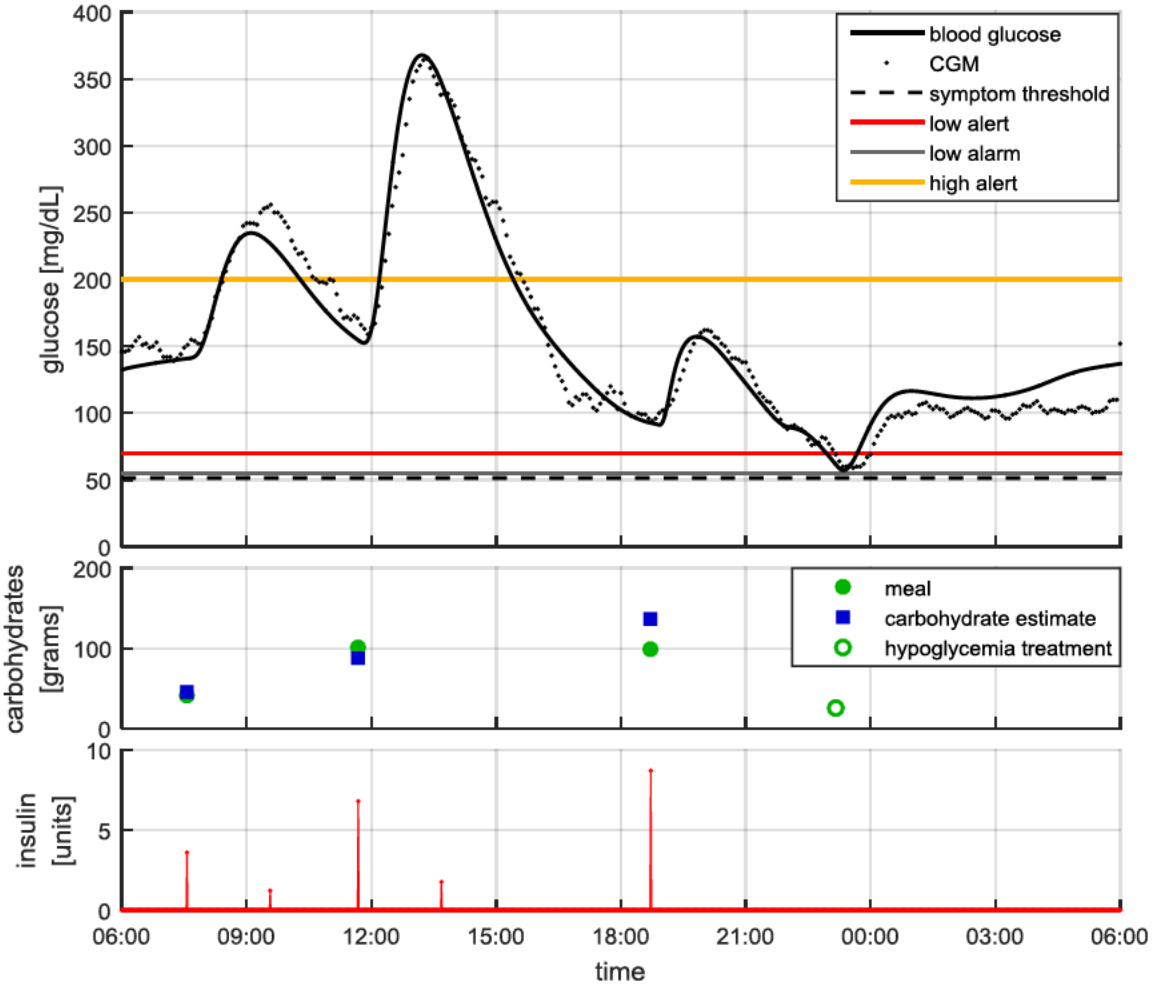
level of 140 mg/dL. Based upon her carbohydrate estimate and CGM reading, the virtual subject administers 3.6 units of insulin (3.1 units to cover the carbohydrates in her meal and 0.5 units to correct for her current glucose). Her trend arrow is flat, so she doesn't make any adjustment to her dose to account for glucose trend.

The virtual subject's simulated blood glucose rises in response to the carbohydrate intake and triggers a high glucose alert at 8:29 AM. Because it has been only one hour since her breakfast bolus, she does not take action in response to the high glucose alert. She checks her CGM two hours after breakfast and sees that her glucose reading is still high (254 mg/dL with a flat trend arrow) so she chooses to take a post-meal correction bolus. Based on her current glucose reading, ISF and target glucose of 120 mg/dL, she calculates a dose of 2.4 units but reduces this by 50% to account for the fact that she has taken an insulin bolus within the last four hours.

By lunchtime, the virtual subject's blood glucose has dropped to 155 mg/dL and her CGM now reads 171 mg/dL with a flat trend arrow. Her lunch contains 100 grams of carbs but she only estimates it to contain 88 grams, so she boluses 5.9 units to cover her carbs and 0.9 units to correct for her elevated glucose reading. Her simulated glucose again rises in response to the carbohydrates in her meal, triggering a high glucose alert at 12:18 PM and peaking around 1:15 PM. Again, she ignores the high glucose alert because it has been less than two hours from her lunch bolus. After two hours, she notes that her CGM reading is still high (338 mg/dL with a diagonal downward trend arrow). She adjusts her current CGM reading by -25 mg/dL to account for her dropping glucose, and takes a correction bolus of 1.8 based on her adjusted glucose estimate of 313 mg/dL and a 50% reduction in calculated dose to account for her insulin on board. This correction bolus helps get her blood sugar closer to her target glucose.

For dinner, the virtual subject has a meal with 99 grams of carbohydrates, but estimates that the meal actually has 137 grams. Her CGM shows a glucose of 96 mg/dL with a flat trend arrow. She calculates an insulin bolus of 9.1 units to cover her estimated 137 grams of carbohydrates but adjusts it down to 8.7 units because her CGM reading is currently below her target glucose by 24 mg/dL (-0.4 units). After dinner, her glucose rises briefly but starts to come back down around 8:00 PM. At 10:00 PM the virtual subject checks her CGM reading before going to sleep. The CGM display shows 88 mg/dL with a flat trend arrow, so she goes to sleep without taking any treatment action. Around 10:30 PM, her glucose begins to drop further, likely as a result of her overestimating the carbohydrate content of her dinner and administering too much insulin. At 11:10 PM, her CGM readings drop to 69 mg/dL, below her low glucose alert setting of 70 mg/dL, triggering an alert. She wakes up and treats her low glucose with 25 grams of fast-acting carbohydrates, and goes back to sleep. These carbohydrates raise her blood sugar, and her blood glucose is maintained between ~110 and 140 mg/dL for the remainder of the night.

Figure 32: Sample blood glucose for one day for one virtual subject



7.3.2.3 Results of Two-week Simulated Study

Overall, 40,000 simulations were run using the simulator for each treatment, with 100 adult virtual subjects and 100 virtual pediatric subjects with varying behavioral characteristics and hypoglycemia symptom thresholds. Results are categorized into two age populations (adults and pediatrics) and two hypoawareness groups (mixed hypoglycemia awareness representing the general population and impaired hypoglycemia awareness). The main results of this simulation are presented below.

7.3.2.3.1 NUMBER OF EVENTS AND DURATION OF TIME SPENT BELOW 50 MG/DL

Simulation data show that the amount of time subjects spent below 50 mg/dL was reduced for the impaired hypoawareness group for both adults and pediatrics when CGM was used for treatment

decisions across all days of sensor wear (Table 28). The results were similar for CGM- and SMBG-based decisions for the mixed hypoawareness group, though the CGM group had a higher percent of virtual subject behaviors with time spent below 50 mg/dL of less than 5 minutes.

Table 28: Time Below 50 mg/dL Across All Days of Sensor Wear

	Mixed Hypoawareness		Impaired Hypoawareness	
	SMBG	**CGM**	**SMBG**	**CGM**
ADULTS				
Median (25th - 75th Percentile) minutes/day	0 (0-1.8)	0 (0-1.4)	3.9 (0-10.3)	1.4 (0-4.6)
% of Virtual Subjects with Time <5 minutes/day	88%	91%	56%	77%
PEDIATRICS				
Median (25th - 75th Percentile) minutes/day	0 (0-0)	0 (0-0.3)	1.4 (0-4.9)	0 (0-2.1)
% of Virtual Subjects with Time <5 minutes/day	95%	97%	76%	92%

Both the average event rate, which is the number of events below 50 mg/dL per virtual subject with a specific behavior per week, and the average duration of the events below 50 mg/dL were reduced with CGM (Table 29).

Table 29: Average Rate and Average Duration of Events Below 50 mg/dL Across All Days of Sensor Wear

	Mixed hypoawareness		Impaired hypoawareness	
	SMBG	**CGM**	**SMBG**	**CGM**
ADULTS				
Average Rate [per VSB-week]	0.57	0.46	1.58	0.95
Average Duration [min] (±SD)	25.94 (±16.99)	21.85 (±11.50)	31.86 (±19.91)	24.64 (±12.52)
PEDIATRICS				
Average Rate [per VSB-week]	0.24	0.23	0.83	0.47
Average Duration [min] (±SD)	26.94 (±20.56)	20.03 (±11.84)	31.24 (±22.64)	22.01 (±13.01)

One potentially higher risk of using CGM for treatment decisions was identified on the first day of sensor wear for pediatric subjects (higher risk was not observed in adult subjects). While the average rates of events below 50 mg/dL and 70 mg/dL were higher for pediatrics making CGM-based treatment decisions, the average duration of these events was noticeably reduced with the use of CGM (Table 30). This suggests that the low alert and alarm with CGM effectively mitigated this risk by decreasing the duration of events in all situations. The increased rates of low glucose events are likely related to a high bias

observed with some sensors in several pediatric patients in the Dexcom Software 505 pediatric clinical study, resulting in an excessive meal or correction insulin dose in the simulations.

Table 30: Average Rate and Average Duration of Events Below 50 mg/dL and 70 mg/dL for Pediatric Subjects on Day 1 of Sensor Wear

		Mixed hypoawareness		Impaired hypoawareness	
		SMBG	**CGM**	**SMBG**	**CGM**
Events below 50 mg/dl	Average Rate [per VSB-week]	0.29	0.46	0.88	0.89
	Average Duration [min] (±SD)	25.76 (±17.58)	21.28 (±11.45)	31.61 (±22.10)	24.41 (±13.01)
Events below 70 mg/dl	Average Rate [per VSB-week]	2.02	2.60	1.98	2.56
	Average Duration [min] (±SD)	55.58 (±36.92)	42.93 (±25.83)	91.60 (±50.58)	55.75 (±33.37)

7.3.2.3.2 TIME SPENT BETWEEN 70-180 MG/DL ACROSS ALL DAYS OF SENSOR WEAR

CGM-based treatment decisions resulted in slightly more time spent in the target glucose range of 70 mg/dL-180 mg/dL for both adult and pediatric subjects (Table 31). This trend was seen for both hypoawareness groups. No safety risks were identified for CGM.

Table 31: Time Spent Between 70 mg/dL and 180 mg/dL

	Mixed Hypoawareness		Impaired Hypoawareness	
Time Between 70-180 mg/dL	**SMBG**	**CGM**	**SMBG**	**CGM**
Adult Median hours/day (25th - 75th Percentile)	15.8 (13.8-18.1)	16.2 (14.4-18.3)	15.6 (13.7-17.9)	16.2 (14.5-18.3)
Pediatric Median hours/day (25th - 75th Percentile)	14.1 (12.0-16.4)	14.3 (12.3-16.5)	14.0 (11.9-16.24)	14.3 (12.2-16.5)

7.3.2.3.3 TIME SPENT ABOVE 250 MG/DL ACROSS ALL DAYS OF SENSOR WEAR

Reducing time spent above 250 mg/dL is important for diabetes management because hyperglycemia can adversely impact HbA1c and result in diabetic ketoacidosis if not controlled. Simulations show that time spent above 250 mg/dL is reduced by non-adjunctive use of CGM relative to SMBG use in both adults and pediatrics (Table 32). Hypoglycemia awareness did not have an impact on this result. No risks of using CGM for treatment decisions were identified.

Table 32: Time Spent Above 250 mg/dL

	Mixed Hypoawareness		Impaired Hypoawareness	
Time >250 mg/dL	**SMBG**	**CGM**	**SMBG**	**CGM**
ADULTS				
Median minutes/day (25th - 75th Percentile)	125.6 (62.6 - 211.8)	119.1 (59.7 - 197.9)	125.2 (62.3 - 212.1)	118.2 (59.7 - 198.2)
% of Virtual Subjects <6 hours/day	67%	70%	67%	70%
PEDIATRICS				
Median minutes/day (25th - 75th Percentile)	212.6 (116.9 - 330.8)	200.2 (112.4 - 309.6)	212.1 (116.3 - 329.6)	200.6 (112.71 - 409.3)
% of Virtual Subjects <6 hours/day	43%	45%	43%	45%

7.3.2.4 Summary of Outcomes

Table 33 provides a summary of the outcomes of this two-week simulation study. Overall, these simulations suggest that in all but one scenario, the risks of non-adjunctive CGM use are similar to SMBG, and CGM offers additional benefits. Risks associated with an occasional increase in hypoglycemic events for pediatric subjects with CGM are mitigated by the presence of alerts. In the highest risk populations, patients with impaired hypoglycemia awareness, CGM performs better than SMBG in reducing severe hypoglycemia without an increase in hyperglycemia.

Table 33: Summary of Outcomes

Glycemic Outcome	Summary of Benefits and Risks of CGM-based Decision Making
Average Event Rate and Time spent below 50 mg/dL	Benefits CGM reduced the rate of events below 50 mg/dL by 19% for adults and 5% for pediatrics with mixed hypoawareness, with the greatest decrease seen in the impaired hypoawareness group (40% reduction for adults and 45% reduction in events for pediatrics). The average duration of events below 50 mg/dL was reduced by 4 minutes in adults and 7 minutes in pediatrics for the mixed hypoawareness group. The impaired hypoawareness group saw average event duration reductions of 7 minutes in both adults and pediatrics. No difference was seen for median time below 50 mg/dL for the mixed hypoawareness group (median time of 0 minutes/day). CGM reduced the time spent below 50 mg/dL for the impaired hypoawareness groups for both adults and pediatrics, with an increase in the number of subjects experiencing <5 minutes/day below 50 mg/dL. Risk The average rates of events below 50 mg/dL were higher for pediatric subjects in both hypoawareness groups only on day 1 of sensor wear but the average event duration was noticeably reduced for all cohorts, indicating that CGM alerts and the alarm are an effective mitigation.
Time spent between 70-180 mg/dL	Benefit CGM resulted in slightly more time in the target glucose range for both awareness groups for both adults and pediatrics. Risk No risks were identified.
Time spent above 250 mg/dL	Benefit CGM decreased the amount of time spent above 250 mg/dL for both adults and pediatrics. Hypoglycemia awareness did not have any impact on this result. Risk No risks were identified.

7.3.3 MEAL DOSING SIMULATION

7.3.3.1 Purpose of the Simulation

Whereas the two-week simulation study examined the overall benefit-risk of non-adjunctive CGM use, this single meal dosing simulation was aimed at identifying specific conditions that may demonstrate increased risk for non-adjunctive use. This was achieved by evaluating the impact of individual parameters and their variation on the glycemic risk of meal-time insulin dosing using CGM and SMBG using a simple Monte Carlo simulation method. Parameters evaluated include physiological parameters such as insulin sensitivity, user behavior errors such as errors in estimation of carbohydrates, and conditions that could impact CGM performance such as reduced calibration frequency or calibrating with a less accurate meter.

7.3.3.2 Simulation Design

Data for this simulation came from CGM and SMBG data obtained from clinical studies to support the regulatory approval of the Software 505 algorithm used in the Dexcom G5 Mobile System. The simulations compared a single meal-time insulin dosing decision based on a CGM glucose value (and trend) to a dosing decision based on a SMBG point value. A baseline simulation was initially run to establish the risk of hypoglycemia and hyperglycemia for both SMBG and CGM under typical dosing conditions. Specific parameters were then modified to understand their impact on hypoglycemic or hyperglycemic risk profiles compared to baseline.

Figure 33 provides an overview of this simulation process. White boxes indicate components that are common to simulations of dosing based on both SMBG and CGM measurements. Yellow boxes are specific to dosing simulations using SMBG measurements, and blue boxes are specific to dosing simulations using CGM measurements. Each simulation consisted of 50,000 simulated subjects with randomly drawn pre-meal blood glucose values and rates of change, insulin sensitivity, and meal carbohydrate contents. CGM and SMBG measurements were then simulated using models of measurement error derived from clinical study data, and carbohydrate estimates were simulated by applying a model of carbohydrate counting errors based on published data (Brazeau et al., 2013).

For each simulated subject, the insulin dose required to cover a meal was calculated based on the carbohydrate estimate and the simulated CGM or SMBG readings (including trend for CGM), using the standard bolus equation and a published dose adjustment to account for glucose rate of change (DirecNet Study Group, 2008). The resulting doses were compared to an optimal dose, calculated from the same bolus equation using the error-free pre-meal glucose level and rate of change and the actual amount of carbohydrates in the meal.

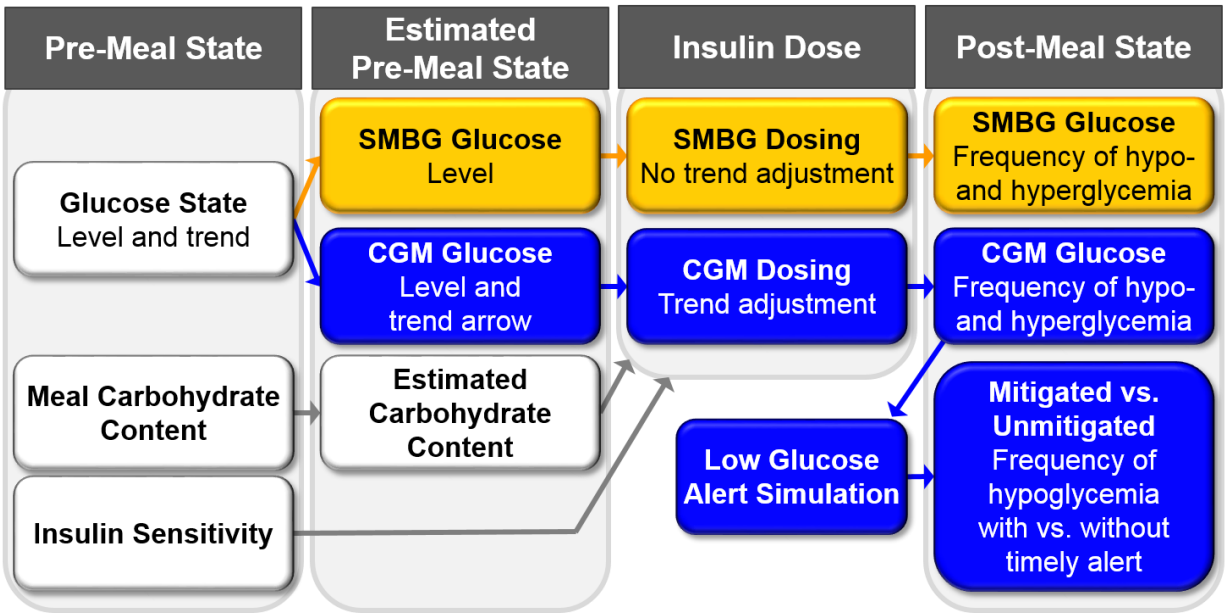
Errors in doses calculated from CGM and SMBG (differences from the optimal dose) were then used to calculate post-meal glucose levels for each treatment group, based on the virtual subject's insulin sensitivity. For CGM-based treatment, CGM low glucose alerts were also simulated to determine what fraction of the post-meal hypoglycemia cases would potentially be mitigated by an alert; alerts provided

within ± 15 minutes of hypoglycemia onset were considered effective mitigation. Simulated outcomes were quantified in terms of the percentage of simulated subjects with post-meal hypoglycemia (<70 mg/dL), before and after considering the effect of low glucose alerts, and the percentage with post-meal hyperglycemia (>180 mg/dL). A more complete description of simulation methods is provided in Appendix 13.1.

Simulation steps included the following:

1. Sample input parameters defining pre-meal state (pre-meal glucose level and rate of change, carbohydrates, insulin sensitivity)
2. Simulate CGM and SMBG measurements (estimated pre-meal state)
3. Calculate insulin doses based on SMBG and CGM
4. Calculate post-meal glucose level for SMBG and CGM based on the dose error for each (comparison to optimal dose) and the subject's insulin sensitivity
5. If post-meal glucose is below 70 mg/dL, simulate CGM low glucose alerts (for CGM-based doses only) and determine whether the alert is expected to mitigate the hypoglycemia, based on alert timing (if provided within ±15 minutes of hypoglycemia onset)
6. For each set of the 50,000 simulated subjects, quantify risk of hypoglycemia and hyperglycemia by calculating the fraction of subjects with post-meal glucose >180 mg/dL (indicating hyperglycemia risk) and the fraction with post-meal glucose <70 mg/dL not mitigated by a low glucose alert (indicating hypoglycemia risk), for the two doses

Figure 33: Meal Dosing Simulation Overview



Hypoglycemia: <70 mg/dL; Hyperglycemia: >180 mg/dL

7.3.3.3 Simulated Conditions

A baseline simulation was initially run to establish the risk of hypoglycemia and hyperglycemia for both SMBG and CGM under typical dosing conditions. Specific dosing conditions (listed in Table 34) were then simulated to understand their impact on hypoglycemic or hyperglycemic risk profiles compared to baseline. Each condition was simulated by replacing the corresponding baseline input (e.g. fixing insulin sensitivity at a high level or low level rather than drawing from a wide distribution), error model (e.g. changing the magnitude of carbohydrate-counting errors), or behavioral parameter (e.g. changing the CGM low alert setting from 70 to 80 mg/dL) with a new value or range of values. The impact of SMBG performance and calibration frequency on CGM-based dosing was assessed by running the Software 505 algorithm on the original clinical data but with altered calibration inputs, and running the meal dose simulation with CGM error models derived from the new algorithm output.

For each simulated condition, the risks associated with determining an insulin dose based on a pre-meal CGM reading (with and without CGM low glucose alerts) were directly compared to the risks associated with dosing based on a pre-meal SMBG measurement. Because hypoglycemia poses the greatest acute risk to a subject, the following results are focused only on the hypoglycemia risk, not hyperglycemic risk.

Table 34: Simulated Conditions to Evaluate Glycemic Risk

Factor	Simulated Condition
Patient Physiology	• Insulin sensitivity (ISF and ICR) • Relationship between ISF and ICR • Errors in insulin sensitivity estimation
User Behavior	• Carbohydrate-counting error • Alert threshold • Erroneous compensation for pre-meal rate of change • Target glucose • Meal size • Calibration frequency
SMBG Performance	• SMBG precision • Systematic SMBG bias • Inaccurate calibration of CGM
Miscellaneous	• Adults vs. pediatric CGM performance • Pre-meal glucose level • Day of CGM wear • Correction bolus (lack of meal)

7.3.3.4 Baseline Simulation Results

The baseline simulation reflects results expected in a typical real-world setting, using inputs, error models and behaviors that are reflective of the full range of possible conditions or derived from previous clinical data and practice. A full list of baseline assumptions is provided in Appendix Section 13.1. Although the baseline simulation is intended to reflect actual use, this simulation assumed an aggressive target glucose level of 100 mg/dL to maximize the risk of post-meal hypoglycemia.

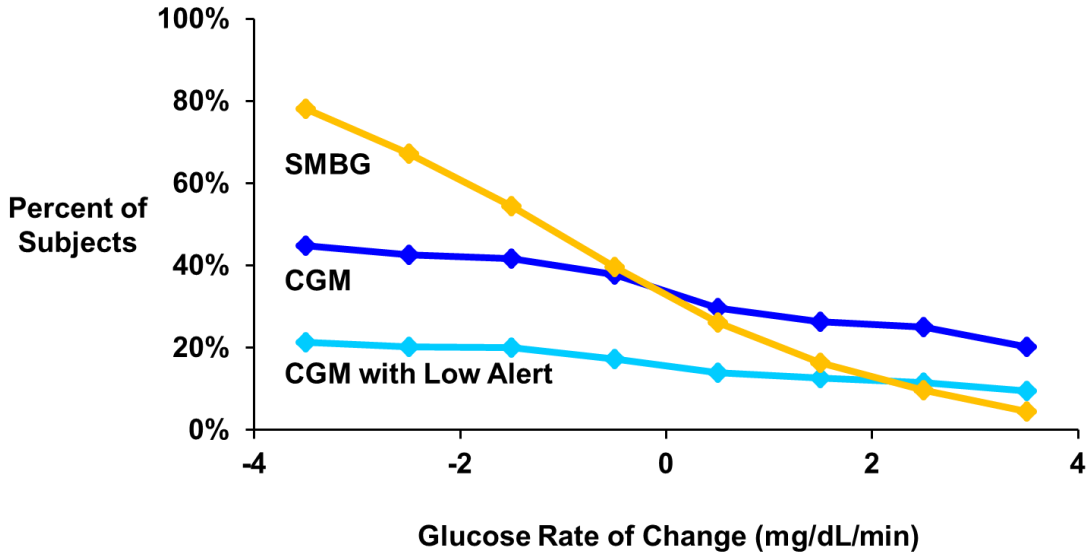
Figure 34 depicts the hypoglycemia risk for the baseline simulation. Recognizing that the use of glucose trend information is a key difference between doses calculated from CGM and SMBG, hypoglycemia risk is presented in relation to pre-meal glucose rate of change. Lower lines on the graph indicate lower overall risk for hypoglycemia and flatter lines indicate more consistent risk across the range of possible pre-meal glucose rates of change. The figure shows that SMBG-based dosing risks were highly dependent on pre-meal glucose rate of change. This reflects the fact that SMBG does not provide glucose trend information, and therefore no dose adjustments can be made to compensate for pre-meal glucose rate of change. In contrast, CGM-based dosing risks were far less dependent on pre-meal glucose rate of change, as evidenced by a flatter line across the various glucose rates of change. The consistent reduction in hypoglycemia risk from CGM-based dosing when adding low glucose alerts, (light blue vs. dark blue line in the figure), demonstrates that CGM alerts and alarms effectively mitigate much of the hypoglycemia risk, across the full range of pre-meal glucose rates of change.

For both SMBG and CGM-based dosing, risk of hypoglycemia was highest for rapidly falling glucose rates of change, though CGM, especially with low alerts, had significantly lower risk than SMBG.

At high positive rates of change, CGM users increased their insulin dose and took more insulin than virtual subjects using SMBG to determine their insulin dose. This resulted in a greater risk of hypoglycemia for CGM users, but CGM alerts reduced the risk from the increased insulin dose to a level that was close to SMBG-based dosing.

As expected, risk of hyperglycemia was higher for larger positive pre-meal rates of change (data not presented) for both CGM and SMBG.

Figure 34: Hypoglycemia Risk in Baseline Condition



Lines depict the percent of simulated subjects whose meal doses resulted in post-meal glucose below 70 mg/dL (indicating risk of hypoglycemia) for each pre-meal glucose rate of change. The dark blue line shows CGM hypoglycemia risk without low glucose alerts, and the light blue line shows the percent of subjects with post-meal hypoglycemia risk after excluding subjects that received a low glucose alert within 15 minutes of hypoglycemia onset.

7.3.3.5 Simulation Results for Other Tested Dosing Conditions

Simulations of a variety of different meal-time dosing conditions demonstrated that the biggest contributors to hypoglycemia risk were incorrect carbohydrate estimates in meals and incorrect estimates of individual insulin sensitivity (Table 35). These risk factors were not related to device errors but to user behaviors, and had a similar impact on the risk associated with SMBG-based and CGM-based dosing. Setting a lower glucose target for insulin dosing and using a meter with systematic high or low bias also resulted in similar increases in hypoglycemia risk for both CGM (calibrated with biased SMBG) and SMBG (used for dosing). For most of the remaining conditions, there were negligible changes in risk compared to the baseline conditions, or reduced risk for both CGM-based dosing and SMBG-based dosing. However, there were three scenarios with increased risk relative to the baseline simulation that were unique to CGM. These unique risks involved incorrect use of trend information, setting alert thresholds at too low of a glucose value, and only calibrating the CGM once every 2 days (instead of the recommended two calibrations per day). The results of these CGM-specific simulations are listed below.

Table 35: Risks Identified

Risk Level Compared to Baseline	Simulated Conditions
Increased Risk for Both CGM and SMBG	Addition of errors in insulin sensitivity estimation Increased carbohydrate counting errors Lower target glucose Larger meals Systematic SMBG bias
Unique Risk for CGM only	Incorrect use of trend information Setting alert thresholds at low glucose values Decreased calibration frequency to 1 time every 2 days

7.3.3.6 Unique Risks Related to CGM

The following three CGM-unique scenarios presented increased risk relative to the baseline simulation.

7.3.3.6.1 IMPACT OF ERRONEOUS ADJUSTMENTS FOR CGM TREND ARROWS

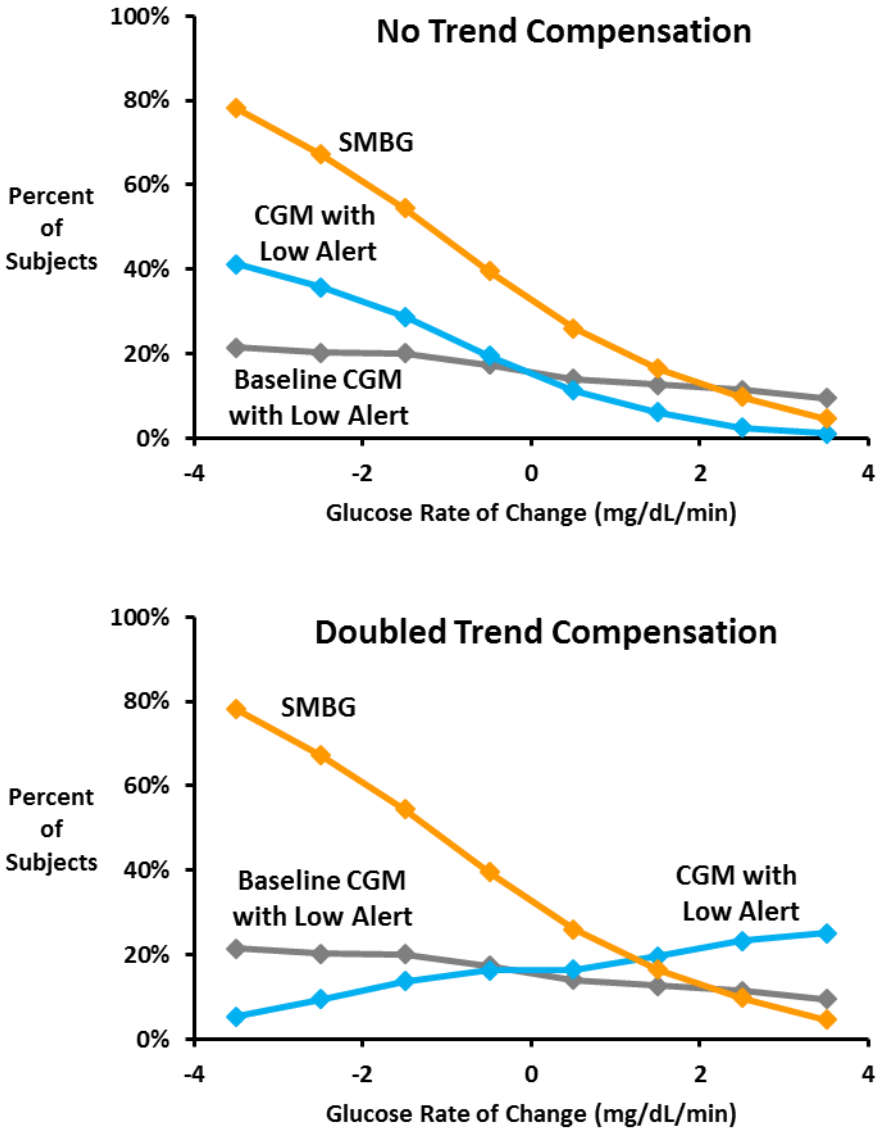
With non-adjunctive use of the Dexcom G5 Mobile System, users will be trained to work with their healthcare professional to determine how to use the CGM trend arrows to adjust their diabetes treatment decisions. Generally, it is likely more insulin will be administered when the trend arrow is pointing up (representing rising glucose) and less insulin will be administered when the trend arrow is pointed down (representing falling glucose). Because users may interpret the CGM trend arrows differently, Dexcom simulated two different trend use scenarios. The first involved no adjustment to the insulin dose based on the glucose trend, which could be the case for a new CGM user and is similar to SMBG-based dosing where only a point value is used for treatment decisions. The second scenario simulated overcompensation for pre-meal glucose trend by doubling the size of dose adjustment; for example, if the appropriate trend-based adjustment for rising glucose is a 20% increase in dose, subjects were assumed to adjust their dose by 40%, and conversely if the appropriate adjustment for a falling glucose was a 20% decrease, the subjects instead decreased the dose by 40%. The simulation results of these two scenarios are shown in Figure 35.

The risks for users who ignore trend information and just use the CGM glucose value when determining an insulin dose show a stronger dependence on pre-meal glucose rate of change than in the baseline dosing condition (appropriate use of trend information). However, the use of CGM alerts reduced the risk relative to SMBG-based dosing in all glucose rates of change.

When a user over-compensated their insulin dose for the CGM trend arrow (doubled trend compensation), an inverse relationship to the baseline scenario was seen. With a rapidly falling glucose, a user would

overcompensate for this and underestimate the amount of insulin needed, contributing to a much lower risk of hypoglycemia compared to both SMBG and the baseline scenario. When the glucose rate of change was highly positive, the risk of hypoglycemia was higher since the user would incorrectly double the size of the insulin dose. This scenario does highlight potential residual risk from over-zealous meal insulin adjustments based on rate of change.

Figure 35: Impact of Erroneous Adjustments for Trend on Hypoglycemia Risk



Lines depict the percent of simulated subjects whose meal doses resulted in post-meal glucose below 70 mg/dL (indicating risk of hypoglycemia), after excluding subjects that received a CGM low glucose alert within 15 minutes of hypoglycemia onset (CGM-based doses only). Grey lines show CGM outcomes from the baseline simulations (appropriate use of trend information) for comparison.

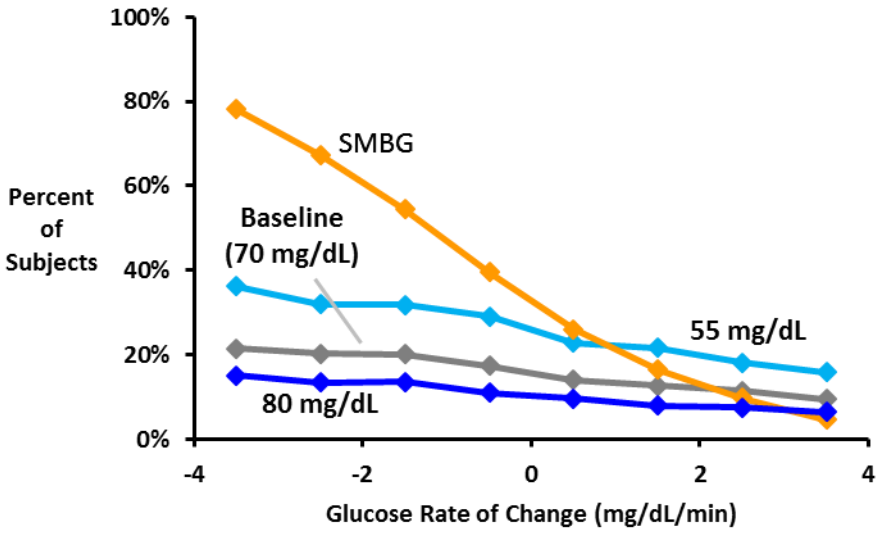
7.3.3.6.2 IMPACT OF CGM ALERT THRESHOLDS

The Dexcom G5 Mobile System has a non-configurable low glucose alarm set at 55 mg/dL. Additionally, CGM has low and high glucose alerts which can be set at a range of glucose levels. To examine the impact of varying alert settings on hypoglycemia mitigation, simulations were run with alerts set at 55 mg/dL (no low glucose alert set, only the low glucose alarm) and the default low glucose alert of 80 mg/dL. Setting the alert threshold at the lowest glucose allowed by the system (55 mg/dL) led to an

increased frequency of potential hypoglycemia compared to the baseline scenario, which assumed an alert setting of 70 mg/dL (Figure 36).

Increasing the alert threshold to 80 mg/dL (the default setting for Dexcom CGM systems) (Figure 36) had the opposite effect: more of the post-meal hypoglycemic events were accompanied by a timely alert. These results suggest that setting the alert threshold to a higher glucose level increases the likelihood that hypoglycemic events caused by mealtime insulin overdose would be mitigated by CGM alerts. This result is consistent with a recently published analysis of the impact of low glucose alert threshold on alert timing relative to hypoglycemia onset (Peyser et al., 2015).

Figure 36: Impact of CGM Low Glucose Alert Threshold on Hypoglycemia Risk



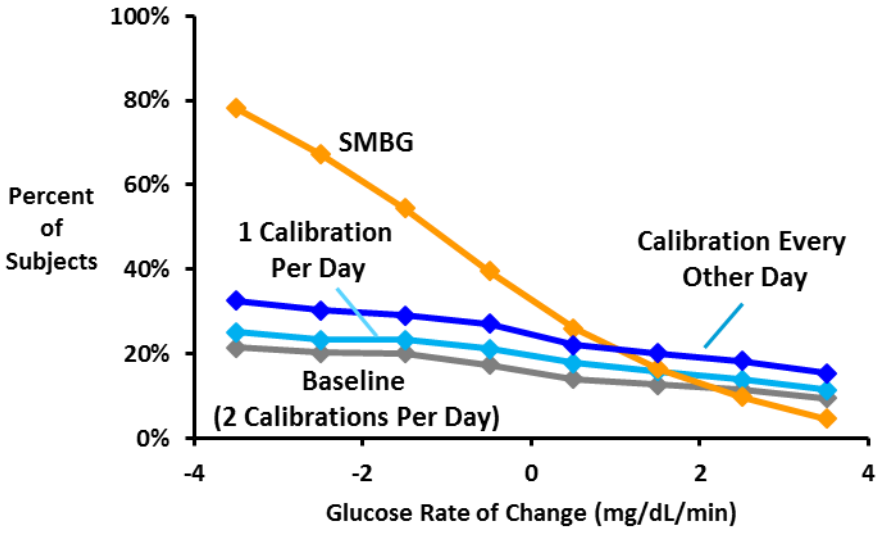
Lines depict the percent of simulated subjects whose meal doses resulted in post-meal glucose below 70 mg/dL, excluding subjects that received a CGM low glucose alert within 15 minutes of hypoglycemia onset (CGM-based doses only). Blue lines show outcomes from CGM-based dosing with different low glucose alert settings, and grey line shows CGM outcomes from the baseline condition simulation (low glucose alert set at 70 mg/dL) for comparison.

7.3.3.6.3 IMPACT OF CALIBRATION FREQUENCY

The recommended calibration schedule for the Dexcom G5 Mobile System is two calibrations at the two-hour startup time, followed by one calibration every 12 hours for the duration of the sensor session. To determine whether users that didn't follow the recommended schedule were at higher risk for post-meal hypoglycemia, calibration schedules were manipulated to approximately half the recommended frequency (one per day) and a quarter the recommended frequency (one per two days).

Calibration frequencies of one per day had little impact on risk, but further reduction in calibration to only once per two days resulted in increased risk of post-meal hypoglycemia (Figure 37). This risk is mitigated by providing prompts to the user to calibrate the device every 12 hours.

Figure 37: Impact of Calibration Frequency on Hypoglycemia Risk



Lines depict the percent of simulated subjects whose meal doses resulted in post-meal glucose below 70 mg/dL, excluding subjects that received a CGM low glucose alert within 15 minutes of hypoglycemia onset (CGM-based doses only). Blue lines show outcomes from CGM-based dosing when simulating reduced calibrations frequencies, and the grey line shows CGM outcomes from the baseline condition simulations (approximately 2 calibrations per day) for comparison.

7.3.3.7 Summary of Findings

This meal dosing simulation was aimed at comparing risk of CGM-based dosing to SMBG-based dosing and identifying specific conditions that specifically increase the risk of non-adjunctive use.

Under typical (baseline) dosing conditions, CGM-based and SMBG-based treatment decisions led to a similar overall frequency of hypoglycemia (post-meal glucose below 70 mg/dL), demonstrating that differences in accuracy between CGM and SMBG did not substantially elevate CGM-based dosing risk. CGM-based dosing resulted in greater consistency of outcomes across the range of possible pre-meal glucose rates of change, due to the availability of trend information to make appropriate dosing adjustments. In addition, CGM low glucose alerts mitigated the majority of post-meal hypoglycemia events, leading to a substantially lower rate of unmitigated hypoglycemia for CGM-based dosing in comparison to SMBG-based dosing.

In nearly all of the specific conditions investigated (Table 34), similar relative outcomes were observed: CGM-based treatment decisions led to fewer unmitigated hypoglycemic events than SMBG-based insulin dosing overall, with the largest risk reductions for subjects with dropping pre-meal glucose. Several conditions that increased hypoglycemia risk were identified, but the majority of these conditions resulted in a similar increase in risk for CGM and SMBG-based dosing (Table 35).

The three conditions found to uniquely elevate risk from CGM-based dosing (Table 35) were related to user behaviors. These behaviors included setting an alert threshold that is very low (e.g. 55 mg/dL), calibrating infrequently (once every two days), and making inappropriate adjustments for trend.

However, hypoglycemia awareness was not included in these simulations, and it is likely that CGM users who choose to remove optional low glucose alerts have sufficient hypoglycemia awareness to mitigate some or all of this added hypoglycemia risk. Inappropriate trend-based adjustments are likely to be corrected over time as a result of the near-term feedback that CGM provides.

7.4 SUMMARY OF SAFETY AND EFFECTIVENESS

Safe and effective use of the CGM technology for diabetes treatment decisions requires that the device is sufficiently accurate and reliable. The performance of the Dexcom G5 Mobile System is well established through Dexcom's clinical studies. The device uses Dexcom's newest algorithm technology, Software 505, and has an MARD of 9% in adults and 10% in pediatrics, compared to the reference glucose in blood plasma (YSI). Additionally, 93% of CGM readings in adults and 91% of CGM readings in pediatrics are within ±20 mg/dL of the paired YSI value at reference levels ≤80 mg/dL or within ±20% at reference levels >80 mg/dL. This accuracy of the Dexcom G5 Mobile System is significantly improved over previous CGM generations.

Based on discussions with the FDA, it was determined that the indication change should be supported by computer simulations to ensure safe and effective non-adjunctive use of the Dexcom G5 Mobile System. Assessing the risk of the proposed expanded use requires an evaluation of hypoglycemic events. However, controlled clinical studies do not fully represent the true benefit-risk profile of a device when it is used in a real-world setting and may not fully assess uncommon and high risk events, such as severe hypoglycemia. Severe hypoglycemia is a rare event in clinical trials and presents an acute risk to patients. Dexcom determined that a simulation approach would provide an effective means to evaluate CGM-based treatment decisions because hypoglycemia can be modeled directly, without exposing patients to any risks of these events.

Dexcom conducted two simulation studies to support the safety and effectiveness of the non-adjunctive indication: the two-week simulation study and the meal dosing simulation. Both simulations allowed Dexcom to compare glycemic outcomes of CGM-based treatment decisions to the standard of care, SMBG-based treatment decisions. Additionally, each simulation modeled CGM and SMBG performance from actual device performance observed in previous clinical studies.

The two-week simulation study was conducted in collaboration with the University of Padova and utilized the UVA/Padova T1D Simulator. The purpose of this simulation was to assess the overall risk and benefit of non-adjunctive use of the CGM compared to SMBG by assessing glycemic outcomes, including time in severe hypoglycemia, time in hypoglycemia and hyperglycemia, and time in target glucose range in pediatric and adult populations.

The meal dosing simulation assessed individual risks associated with CGM and user behavior, compared to SMBG. This simulation used a simplistic model for single meal-time dosing and was intended to identify specific situations that could result in high risk (hypoglycemia and hyperglycemia) with non-adjunctive CGM use. It was designed to represent a single decision (not two-weeks of wear) made by

CGM versus one made by SMBG. This study considered differences between CGM and SMBG technology that could influence user behavior and glycemic outcome, such as the use of CGM trend information, alerts and alarms, calibration frequency, and SMBG frequency.

The combination of these two simulations in conjunction with existing clinical data on device accuracy provided a comprehensive assessment of the safety and effectiveness of the Dexcom G5 Mobile System when used for diabetes treatment decisions.

Effectiveness of non-adjunctive use was demonstrated by improved glycemic outcomes for CGM-based treatment decisions compared to SMBG. The two-week simulation study showed a reduction in time spent above 250 mg/dL, slightly more time in the target glucose range, and equivalent or less time below 50 mg/dL when CGM was used for treatment decisions. The average rate and average duration of events below 50 mg/dL was also reduced.

Of the observed improvements in glycemic outcomes, CGM-based treatment decisions were most effective in reducing the incidence of severe hypoglycemia (<50mg/dL) in subjects with impaired hypoglycemia unawareness, who are particularly vulnerable to severe hypoglycemia. A lower incidence of severe hypoglycemia was seen in all cases for CGM-based treatment decisions compared to SMBG-based decisions except in simulations modeling day one sensor wear in pediatric subjects. Although the number of these events on the first day of sensor wear in pediatrics was higher, the duration of the events was reduced due to the CGM low glucose alert and alarm.

Overall, the two-week simulation demonstrates that CGM-based decisions are safe, in all but one scenario the risks of non-adjunctive CGM use are similar to SMBG, and CGM offers additional benefits, such as alerts. Risks associated with an occasional increase in hypoglycemic events for pediatric subjects with CGM are mitigated by the presence of alerts.

The meal dosing simulation demonstrated that for most of the conditions simulated, there were similar risks between CGM-based dosing and SMBG-based dosing. Individual parameters, such as increased errors in insulin sensitivity information, increased carbohydrate counting errors, lower target glucose, larger meals, and systematic SMBG bias increase risks for both CGM- and SMBG-dosing but do not result in increased risks for CGM-based treatment decisions compared to SMBG. However, there were three scenarios with increased risk relative to the baseline simulation that were unique to CGM. These unique risks involved:

- Incorrect use of trend information (overcompensating in an attempt to prevent hyperglycemia, thereby causing hypoglycemia)
- Setting low alert thresholds at too low of a glucose value
- Only calibrating the CGM once every two days (instead of the recommended two calibrations per day)

The recommended calibration schedule for the Dexcom G5 Mobile System is two calibrations at the two-hour startup time and one calibration every following twelve hours. Reduced calibration frequencies of

one per day had little impact on risk, but further reduction in calibration to only once per two days (i.e., every other day) resulted in increased risk of post-meal hypoglycemia. This risk is mitigated by providing prompts to the user to calibrate the device every twelve hours. Both the receiver and app provide these prompts, reminding the user to calibrate.

The results suggest that setting the low alert threshold to a higher glucose level increases the likelihood that hypoglycemic events caused by meal-time insulin overdose would be mitigated by CGM alerts. This result is consistent with a recently published analysis of the impact of low glucose alert threshold on alert timing relative to hypoglycemia onset (Peyser et al., 2015).

In summary, the two distinct computer simulations, along with existing clinical performance and safety data for the Dexcom G5 Mobile System, establish a reasonable assurance of safety and effectiveness for the expanded non-adjunctive use indication.

Safe and effective use of the system requires that users follow the IFU for the Dexcom G5 Mobile System. The IFU warns patients to calibrate the device every twelve hours, instructs on how to set alerts, and explains how to use trend information (with frequent reminders not to take too much insulin in response to rising glucose).

More information on the instructions for safe and effective use of the Dexcom G5 Mobile System is provided below.

8 PATIENT AND CLINICIAN EDUCATION

The clinical evidence for the adjunctive use of CGM and the simulations supporting non-adjunctive use show that CGM can be used safely to make treatment decisions. Therefore, Dexcom plans a product training program to inform users of the appropriate ways to optimize their CGM-based treatment decisions and when users should not use CGM for treatment decisions using existing information from the current, commercial Dexcom G5 Mobile System instructions and revised information for CGM-based treatment decision (Table 36).

The training provides patients several options and methods for product training that best fit their individual needs. In addition, Dexcom plans to ensure that healthcare professionals are trained and have similar resources on Dexcom products and training.

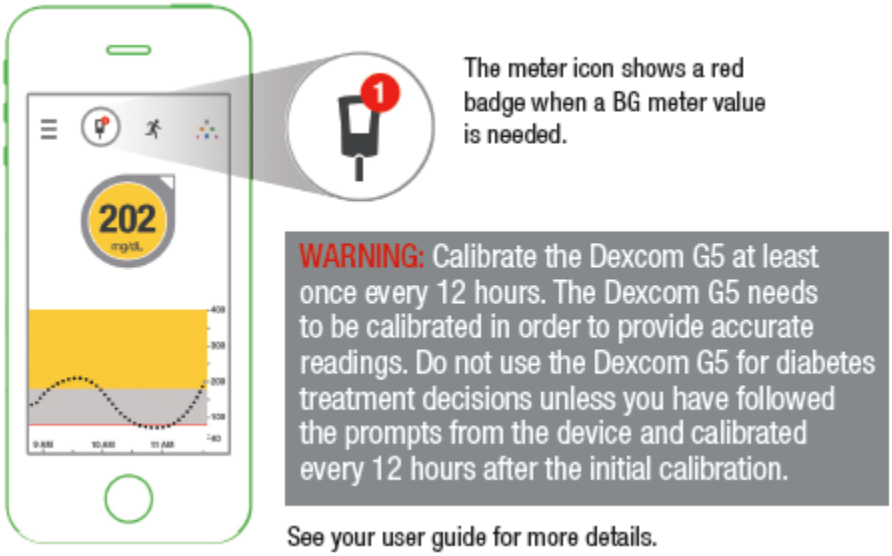
Table 36: Key Training Information

Revised Key from Current, Commercial Instructions Relevant to CGM-based Treatment Decisions	**New Keys for Making CGM-based Treatment Decisions**	**New Information When SMBG is Required/ When Not to Treat with CGM**
Calibration every twelve hours	CGM reading Trend arrow Calibration with SMBG every twelve hours	Calibration Symptoms do not match CGM readings Taking acetaminophen No CGM reading No arrow

8.1.1 REVISED KEY INFORMATION FROM CURRENT, COMMERCIAL INSTRUCTIONS

The instructions also rely on existing information from the current, commercial G5 Mobile System. The revised instructions remain very similar to the existing instructions. One instruction is particularly relevant to CGM-based treatment decisions. This is the requirement to calibrate every twelve hours. Calibration helps provide accurate CGM readings, and this accuracy is important for CGM-based treatment decisions. Dexcom has retained the existing instructions on calibration with slight modifications related to non-adjunctive use (Figure 38).

Figure 38: Example of Calibration Warning in the Getting Started Guide



8.1.2 NEW KEY INFORMATION IN REVISED INSTRUCTIONS

Basic use of the Dexcom G5 Mobile System in diabetes treatment decisions will be similar to SMBG in that the CGM provides a point glucose reading on which to base treatment decisions. CGM also provides glucose trend and rate of change information, which can help a patient make a more informed treatment decision. Instructions on how to use this CGM-specific information is highlighted in the new training materials.

The revised instructions explain that in order to make CGM-based treatment decisions the user needs (Figure 39):

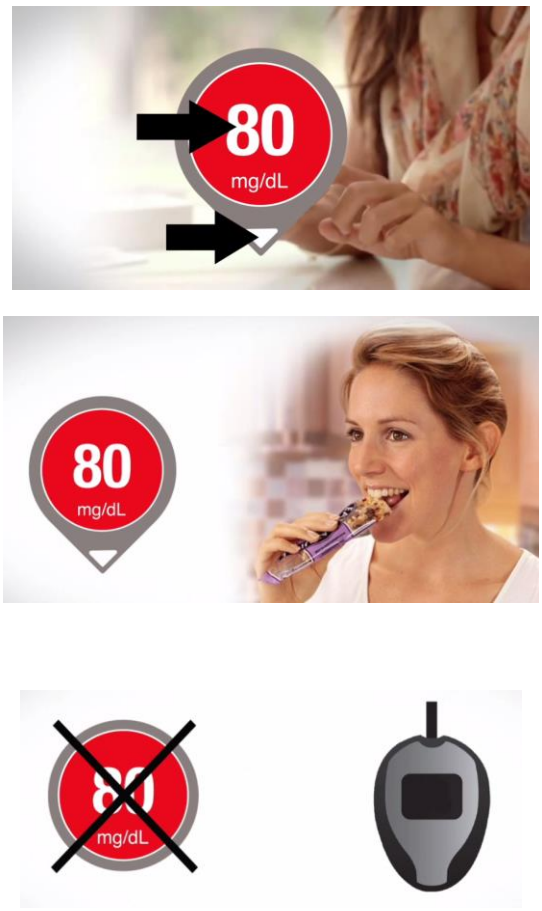
- A CGM reading (number);[11]
- A trend arrow

The CGM reading provides a point glucose value, like an SMBG value, on which to base treatment decisions. The arrows serve two purposes. First, their presence indicates that the system has adequate information to rely on the reading. This means the system has a history of consistent readings that suggest the sensor is accurate and not "noisy." Second, their presence provides additional information to inform treatment decisions, such as the speed and direction of glucose change (e.g., rapidly increasing versus remaining stable). Note that there are situations where an arrow is not present but a CGM reading is

[11] "Number" is the layman's term used in the instructions to help users remember a CGM reading is required. The CGM reading is the number in units of mg/dL.

present. In these situations, there is adequate information to rely on the CGM reading for alerts and trending, but there is inadequate information to make CGM-based treatment decisions.

Figure 39: Screenshots from Interactive Training Tutorial



Top: CGM reading (number) and arrow. Middle: reading and arrow needed to make treatment decision (eating). Lower: absence of arrow indicates SMBG for treatment decisions.

The instructions inform the user that SMBG is still required:

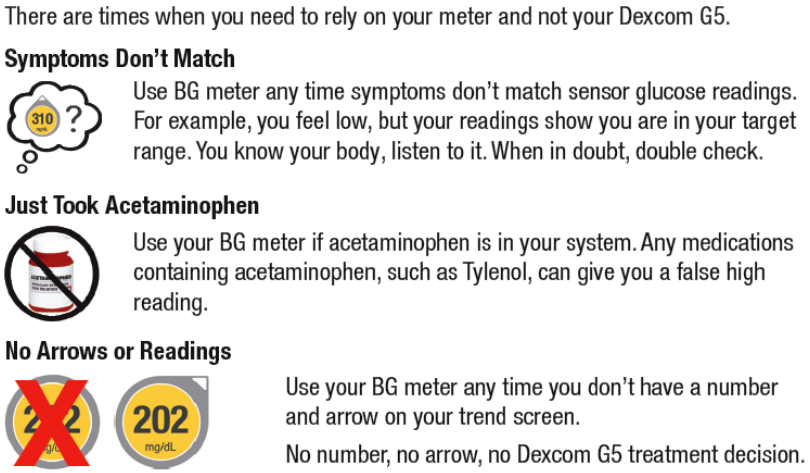
- For calibration
- At times when the CGM information is incomplete or potentially unreliable

To clarify these times when the CGM information is incomplete or potentially unreliable, the instructions specifically emphasize three instances where users should not treat based on CGM readings (Figure 40):

- When symptoms or expectations do not match the CGM reading
- When the user has taken acetaminophen
- When a CGM reading is missing or when a trend arrow is missing

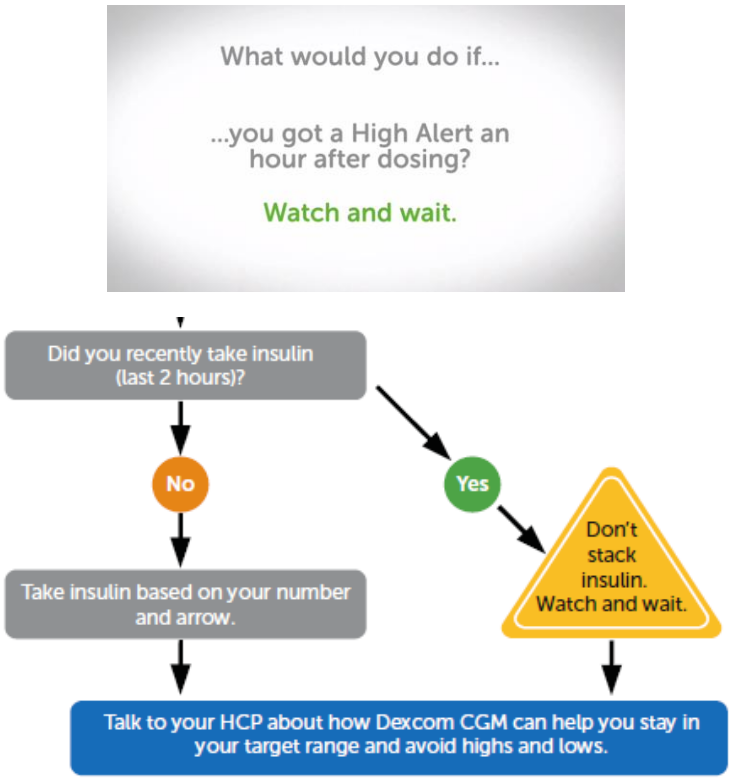
Although there might be enough information to use CGM alerts and trending in these three instances, there is inadequate information to make CGM-based treatment decisions.

Figure 40: Getting Started Guide Showing When Not to Use CGM for Treatment Decisions



Since a patient could use the CGM information to dose insulin, the instructions also inform the user about the risks of stacking insulin (Figure 41). Insulin stacking occurs when a user administers an insulin bolus while the previous insulin bolus is still active, which increases risk for hypoglycemia.

Figure 41: Screenshot from Interactive Training Tutorial (top) and Getting Started Guide (bottom) Regarding Stacking Insulin



The key CGM information required for making treatment decisions (reading and arrow) and times when not to use CGM were designed to be simple and easy to remember because this is the most important information for using the device safely. The instructions also provide guidance on how users may work with their healthcare professionals to gain further intuition about their glucose levels and use that to inform their treatment decisions. For example, the instructions show that when users see the "up arrow" they may choose to take a little more insulin than they would for the number alone. The instructions do not state how much "a little more" is because the amount of insulin needed varies by individual and should be determined by working with a healthcare professional.

8.1.3 FORMAT OF REVISED INSTRUCTIONS

Dexcom revised the Dexcom G5 Mobile System's IFU to focus on the important information related to CGM-based treatment decisions and remove redundancy. Dexcom added a new chapter focused on CGM-based treatment decisions to the User Guide and a new section to each of the Getting Started Guide and Interactive Training Tutorial. In addition, information for non-adjunctive use is included where relevant in all IFU material, outside of the new chapter and sections. The instructions are the same for naïve and experienced CGM users, and both parties were tested (Section 9).

Dexcom plans to provide a product training program for patients with several options for product training to allow users to select the method that best fits their individual needs. In addition, Dexcom plans to ensure that healthcare professionals are trained and have similar resources on Dexcom products and training (Table 37).

Table 37: Methods of Training

Product Instructions for Use	• Getting Started Guide (printed in receiver kit) • Interactive Tutorial (video on USB card in receiver kit and online) • User Guide (electronic or printed by request) • Brief package inserts in sensor kit and receiver kit
In-app Training	• Users are required to view screens during initial setup of Dexcom G5 Mobile App
Dexcom Patient Care one-on-one and group patient training	• Webinars • Phone, email, text communication
Additional web-based materials	• Case-based examples
Education for healthcare professionals	• Account training • Printed materials • Online materials

Dexcom's comprehensive training strategy includes five main methods:

1. **Product IFU** will be shipped to each patient in the receiver box and available online.
    a. The primary product instructions include the Getting Started Guide and the interactive tutorial, both of which were validated through the Human Factors Studies for either one-on-one training or self-training (see Section 9). Both the printed Getting Started Guide and a USB card containing the tutorial video are included in the initial receiver kit. The tutorial may be viewed on a personal computer via the USB card or users can locate it on the Dexcom website. These documents are provided in the briefing materials; the tutorial is included on the disc. Reviewers who would like to view only the new section of the tutorial focused on CGM-based treatment decisions may use the Menu button at the top right to scroll to "Using CGM for Treatment Decision" and "Treatment Decisions Video" followed by three case-based questions to test users' understanding of CGM-based treatment decisions.
    b. An electronic user guide/e-book will be available for all users. It provides a comprehensive product reference. Users can download the user guide through the Dexcom G5 Mobile App or through the Dexcom website. Users may also request a free printed copy by mail or through an online request form.
    c. Brief package inserts will be included in the receiver box and the sensor boxes. Sensors are the disposable component of the system, and current users are likely to receive a new sensor box before they would receive a new receiver. These inserts concisely describe the most important details of the keys for treating with CGM (reading and arrow) and when not to treat with CGM. The inserts direct users to where they can find the full training materials. The inserts are designed to grab the attention of users who might otherwise decline to train.
2. The Dexcom G5 Mobile app includes **in-app training** that reinforces how to properly set-up and start the CGM system and includes the key contraindications and safety information that patients need to know about the product. After a user downloads and launches the app for the first time, the in-app training begins, requiring each new patient to view the in-app training.
3. In addition to one-on-one training with their healthcare professional or self-training with the tutorial, Dexcom offers remote product training with the **Patient Care Team**, a group of certified diabetes educators (CDEs) available to help patients get started on their device and answer any product education questions. The Patient Care Team provides one-on-one remote product training via Skype or the telephone as well as group education classes for both beginner and more advanced CGM users. The Patient Care Team reaches out to known[12] new users by phone call, email or text within three days of the initial shipment and contacts new users again at specified

[12] Due to the use of third party distributors and pharmacies, Dexcom may not have immediate knowledge of all new users. All new users (known or unknown) receive a card in their first receiver kit informing them of the Patient Care team and how to contact Patient Care.

intervals (2 weeks, month, 3 months). Users may call Patient Care directly as well. The Dexcom Patient Care Team is available Monday-Friday 8am-5pm PST and can be reached at 1-877-339-2664. Dexcom's Technical Support team is available 24-hours a day, seven days a week for any immediate product questions, complaints or troubleshooting needs at 1-877-339-2664.

4. Dexcom will provide additional **web-based** materials for patients, families, and care givers to provide more context to the training. These programs will include case-based examples on how to use the CGM and make treatment decisions based on the CGM and when to based decisions on SMBG. These materials will be available on the Dexcom website as well as other websites.
5. Finally, **education and tools for healthcare professionals** will be available to support education efforts around CGM and CGM-based treatment decisions. Dexcom provides account training for healthcare professionals. These tools will help facilitate ongoing training for the healthcare professionals and will closely mirror the education developed for patients. In addition, healthcare professionals may view reports provided by the CLARITY System (Section 3.1), which retrospectively identifies patterns and issues in a user's CGM history.

8.1.4 EDUCATION FOR CURRENT USERS

Dexcom plans multiple methods to inform current users who are familiar with CGM that training is available on CGM-based treatment decisions:

- Concise insert in sensor box
- Email
- Postal mail
- Notifications through G5 Mobile App
- Dexcom website
- Banner ads
- Informing distributors
- Patient Care communications (inbound calls for other reasons)

Dexcom will contact known current users through email and postal mail to inform them of training opportunities, including printed and online materials, training with Dexcom Patient Care or training with their healthcare professional. Dexcom will also provide notifications through the Dexcom G5 Mobile App. To accommodate for users who have changed addresses without informing Dexcom or for those who purchase through a third party, Dexcom will also post information on the Dexcom web page and on banner ads. Because every continuing Dexcom customer orders sensors, inserts that describe key information about treatment with CGM will be included in all sensor boxes. These inserts are designed to be concise in order to grab the attention of users who might otherwise decline to train. Dexcom's Patient Care team will provide group training by webinar for current users to learn about the revised indication and instructions, and Patient Care will inform users who call Dexcom for any other reason.

9 HUMAN FACTORS USABILITY STUDY

Human factors usability testing of the Dexcom G5 Mobile System was designed in accordance with the FDA Guidance for Industry titled "Applying Human Factors and Usability Engineering to Medical Devices," issued February 3, 2016. Usability testing evaluated the new IFU and pertinent sections of the safety statements for clarity and ability to support safe and effective non-adjunctive use of the Dexcom G5 Mobile System. Prior to the summative validation study described in this section, four formative evaluations were conducted to improve the design and content of the IFU. Multiple iterations of training materials were evaluated for clarity and completeness in the formative studies. Through the formative process, the final IFU were optimized to inform users when they can and cannot use CGM for treatment decisions.

The summative validation study evaluated the efficacy of the two primary methods of training: the Interactive Training Tutorial as the primary training tool for users who choose to self-train at home and the efficacy of the Getting Started Guide when used in conjunction with a health care professional in one-on-one training. Three user groups, adults, pediatrics and caregivers of young children with diabetes, were assessed on their retention of critical knowledge from training. The study included a subset of participants from each user group that did not receive training to reflect a worst case scenario where current Dexcom CGM users are informed about the new indications for use but do not receive training.

In order to identify critical tasks, hazards and potential use errors related to the new indications for use of the Dexcom G5 Mobile System, Dexcom performed a risk analysis focusing on new risks associated with non-adjunctive use. The new risks identified were used to create scenarios that evaluated users' understanding of critical knowledge of the Dexcom G5 Mobile System. Participants were tested on six scenarios evaluating their comprehension on three critical risks:

Risks:

1. Using CGM for diabetes treatment decisions without a number and arrow
2. Using CGM for diabetes treatment decisions when symptoms do not match the CGM reading
3. Insulin Stacking

Scenarios:

1. Using CGM values to determine a treatment decision under nominal conditions
2. Risk of insulin stacking with SMBG (insulin stacking occurs when a user administers an insulin bolus while the previous insulin bolus is still active, which increases risk for hypoglycemia)[13]
3. User's symptoms do not match CGM value
4. Using CGM values to determine a treatment decision with an error message present
5. Risk of insulin stacking with CGM

[13] This scenario was provided as a baseline for scenario 5. It is focused on the risks for the current SMBG standard of care, not the proposed CGM indication.

6. Using CGM values to determine a treatment decision when no trend arrow is present due to potentially inaccurate sensor glucose readings

These scenarios were designed to test users' comprehension of critical knowledge of when they can and cannot use CGM for treatment decisions based on the three risks outlined above.

9.1 METHODS

The study consisted of one-on-one sessions with participants, in which the participants were presented with scenarios to test their retention of critical knowledge related to non-adjunctive use of the Dexcom G5 Mobile System. The participants received an explanation of the study conduct and its requirements and had an opportunity to have questions answered before beginning the study session. The study involved simulated use of the CGM application as the user's display device.

A prototype version of the Dexcom G5 Mobile app was used for initial setup during training as well as to display specific glucose readings, trends or events that pertained to the training and test scenarios. Each participant was then presented with a series of scenarios and was asked to interact with the CGM system.

The study included a total of 49 participants, divided into the following three user groups that are representative of the user population.

- User Group 1: Adults (age 18 and older) with diabetes on intensive insulin therapy (n = 16)
- User Group 2: Children and adolescents who independently manage their diabetes and are on intensive insulin therapy (approximately age 12 to age 17) (n = 17)
- User Group 3: Caregivers who manage the diabetes care for children on intensive insulin therapy (n = 16)

The sample size for this study follows Appendix B, Considerations for Determining Sample Sizes for Human Factors Validation Testing from FDA guidance. The goal of human factors validation testing is to identify usability issues, not provide statistical significance for how many users would experience these issues. Research by Faulkner (2003) suggests that a sample size of 15 per user group will detect a minimum of 90% and an average of 97% of all usability issues. Therefore, a minimum of 15 participants per user group was used for this study.

Participants were trained using one of the three methods.

- Self-training with the interactive training tutorial (n = 19)
- One-on-one training with the Getting Started Guide (n = 21)
- No formal training (n = 9)

Of the 40 trained participants, 19 were CGM naïve and 21 were CGM experienced. The "no formal training" method was intended to be a subset, not a defined user group, and was added in consultation with FDA. All nine users who did not receive training were experienced Dexcom CGM users.

Participants in the study were all on intensive insulin therapy, as these users comprise the largest majority of CGM users and have the greatest risk from using CGM. Intensive insulin therapy was defined as using at least one long-acting insulin (i.e. Lantus or Levemir) and three or more injections of short-acting insulin (i.e. Humalog, Novolog, or Apidra) or predominant use of an insulin pump.

The use scenarios included in this Summative Human Factors Usability Study were designed to allow the participants to use the Dexcom G5 Mobile System Mobile App independently and in as realistic a manner as possible, without guidance, coaching, praise, or critique from the study moderator. The use scenarios were designed to incorporate all critical tasks related to the non-adjunctive use of the system.

9.2 RESULTS

The results reported are separated between participants who received training and those who did not receive training on non-adjunctive use of the device (Table 38).

Table 38: Summative Human Factors Usability Scenarios

	Trained Participants (n=40)		Untrained Participants (n=9)	
Scenario	**Total successful outcomes**	**Total failures**	**Total successful outcomes**	**Total failures**
Using CGM Values to Determine a Treatment Decision – Nominal Conditions	40	0	9	0
Risk of Insulin Stacking with SMBG [14]	33	7	9	0
User's Symptoms Do Not Match the CGM Value	40	0	8	1
Using CGM Values to Determine a Treatment Decision – Error Message Present	40	0	9	0
Risk of Insulin Stacking with CGM	40	0	9	0
Using CGM Values to Determine a Treatment Decision – No Trend Arrow Present due to Potentially Inaccurate Sensor Glucose Readings	39	1	6	3

Results, trained participants

The 40 participants who received training by either method achieved a high success rate across the five scenarios that relate to risks using CGM for treatment decisions (Scenarios 1, 3, 4, 5, and 6). No failures were observed in naïve users or in users who received self-training with the tutorial. No failures were observed in trained pediatric users. Only one failure by one CGM experienced participant was observed in the CGM-based scenarios; this participant received one-on-one training. In addition, seven failures were observed in a single scenario focused on SMBG. All failures for the trained group are discussed below.

[14] Note that this scenario relates to failures with the standard of care, SMBG rather than the CGM device being reviewed by the panel

Scenario 2, Risk of Insulin Stacking with SMBG

Seven failures were observed in Scenario #2, Risk of Insulin Stacking with SMBG. Note that this scenario relates to failures with the standard of care, SMBG, rather than the CGM device being reviewed by the panel. Five of these failures were the result of users stating that they would dose a full insulin correction dose for a high blood sugar one hour after eating a meal, resulting in stacking insulin. Taking additional insulin so soon after the initial dose would put these users at risk for hypoglycemia. One failure was the result of a user stating that he wanted to avoid insulin stacking; however, he would still give a full correction dose. This represents an unrecognized misunderstanding of the concept of insulin stacking and his action could cause potential harm. One failure was the result of abnormal use; the participant understood the concept of insulin stacking but chose to administer a full correction dose anyway and potentially put himself at risk of hypoglycemia.

Scenario 6, Using CGM Values to Determine a Treatment Decision – No Trend Arrow Present due to Potentially Inaccurate Sensor Glucose Readings

One failure of trained participants was observed in Scenario #6, Using CGM Values to Determine a Treatment Decision – No Sequential Readings Present due to Potentially Inaccurate Sensor Glucose Readings. The participant, who was a CGM-experienced adult that received formal one-on-one training, stated that she would calculate her insulin dose based on a potentially inaccurate CGM reading. Specifically, she stated that she would test her blood sugar with a fingerstick, calibrate her CGM system and determine her insulin dose based on the calibrated CGM value instead of the fingerstick value. In the context of this study, the response is considered a failure; however, as she did state that she would test with her meter her overall behavior is considered low risk. Additionally, she remembered from training that she was required to have a number and arrow to determine a diabetes treatment decision based on CGM data, but she did not follow those instructions for this scenario.

Results, untrained participants

82.5% of participants who did not receive training were successful in responding to the five scenarios that relate to risks using CGM for treatment decisions. No failures were observed in the scenario focused on SMBG.

Adolescent participant

One participant, a teenage girl, who had been previously informed by her endocrinologist to use her current CGM system for treatment decisions, failed scenarios 3 (symptoms do not match CGM value) and 6 (using CGM values to determine treatment—no sequential readings present) as she reported that she always uses her CGM system to determine her course of action without questioning the accuracy unless she has extreme low or high values that do not match her symptoms. In scenario 3 (symptoms do not match CGM value), she reported that if her CGM

was in range but she felt shaky and sweaty she would ignore the value and go to sleep unless she continued to feel symptomatic and would then consume crackers to "feel better." In scenario 6 (using CGM values to determine treatment—no sequential readings present), she reported that she would use the CGM value (without an arrow) to determine her insulin dose as that is how she currently manages her diabetes. She reported being familiar with scenarios like this in her current diabetes management.

Scenario 6, Using CGM Values to Determine a Treatment Decision – No Trend Arrow Present due to Potentially Inaccurate Sensor Glucose Readings

Two participants, an adult and a caregiver, failed scenario 6. Both participants reported that they would use the CGM value with no arrow to determine an insulin dose and that they currently use the CGM system in a non-adjunctive manner. The adult reported that he only checks with his meter 1-2 times per day for calibration except on Day 1 of sensor wear when he has noticed that the values can be off. The caregiver reported that although she understands that she is not supposed to use the CGM value for treatment decisions today, she does so anyway. She currently takes SMBG measurements with each meal and uses those SMBG values to establish trust with the CGM system.

9.3 USABILITY DISCUSSION

Based on the usability testing performed in the Summative Usability Study, the critical knowledge is effectively communicated in the training and IFU, and critical risks from non-adjunctive use of the Dexcom G5 Mobile System are largely mitigated. All participants who received training, including self-training, were asked at the end of their testing session to recall the information required to determine a diabetes treatment decision on the CGM display device and 100% correctly remembered the requirement of needing a number and an arrow.

The results of the study suggest that there are no significant differences between the two training methods: self-training and one-on-one training. The 40 participants who received training by either method achieved a high success rate across the five scenarios that relate to risks using CGM for treatment decisions (Scenarios 1, 3, 4, 5, and 6). Notably, no failures were observed in the populations that have a high risk of using CGM non-adjunctively: pediatric and naïve users and users who self-train with the tutorial. Only one failure was observed in the CGM-based scenarios; this CGM-experienced adult participant received one-on-one training (Table 39).

Table 39: Overall Efficacy of Training on CGM Errors (40 trained participants; 5 CGM scenarios)[15]

Training Method	Naïve (n=19)	Experienced (n=21)
Self-training with tutorial (n=21)	100% (n=9)	100% (n=12)
One-on-one training (n=19)	100% (n=10)	98%[16] (n=9)

Table 40 shows the three risks identified with non-adjunctive CGM use. Of these three risks, one failure was observed in a scenario where a CGM reading with no arrow was present. The participant, who was a CGM experienced adult and received formal one-on-one training, stated that she would calculate her insulin dose based on a potentially inaccurate CGM reading. Specifically, she stated that she would test her blood sugar with a fingerstick, calibrate her CGM system and determine her insulin dose based on the calibrated CGM value instead of the fingerstick value. In the context of this study, the response is considered a failure; however, as she did state that she would test with her meter her overall behavior is considered low risk.

Table 40: CGM Risks Identified in Trained Users (n=40)

Risks of Using CGM for Treatment Decisions	Response	
	Correct / Total	%
Without a number and arrow	119 / 120	99%
When symptoms do not match CGM reading	40 / 40	100%
Insulin stacking (CGM)	40 / 40	100%

A subset of nine participants who did not receive any training achieved a lower success rate across the five scenarios that relate to risks using CGM for treatment decisions (Table 41). This is not unexpected as these users did not receive any information on when they can and cannot use CGM for treatment decisions.

[15] Percentages were calculated based on the overall success rates of the 40 participant who received training on their responses to the 5 tasks related to CGM risks. The scenarios tested in the study that related to risks of using CGM non-adjunctively were mapped to these risks.
[16] Nine participants with 5 CGM scenarios results in 45 tests. One participant failed one scenario resulting in 98% rate for this combination.

Table 41: CGM Risks Identified in Untrained Users (n=9)

Risks of Using CGM for Treatment Decisions	Response	
	Correct / Total	%
Without a number and arrow	24 / 27	89%
When symptoms do not match CGM reading	8 / 9	89%
Insulin stacking (CGM)	9 / 9	100%

There have been concerns about the risks from stacking insulin based on the frequent glucose data and trend information a CGM user would have. Stacking insulin is not unique to CGM use. Importantly, this study confirms the IFU materials are adequate to mitigate insulin stacking from non-adjunctive CGM use.

The results of this study demonstrate that risks of non-adjunctive use are mitigated through training; there were no comprehension-based errors in pediatric or naïve users or users who self-trained and only one failure in one adult user who was CGM experienced and received one-on-one training. The failure observed has low risk to the user as that although she stated she would dose insulin based on a potentially inaccurate CGM value, she did test her blood glucose with a fingerstick.

There remains some residual risk from non-adjunctive use of the device. If patients do not receive or participate in training on non-adjunctive use of the device, they may misunderstand when they can and cannot use the CGM for diabetes treatment decisions. Three participants who were untrained were already using CGM non-adjunctively, one reportedly on the recommendation of their clinician. These participants did not receive adequate instructions on when to use CGM information for treatment decisions and when to rely on a fingerstick. Dexcom cannot provide training to users or clinicians about proper non-adjunctive use without an approved indication for non-adjunctive use. Therefore, this study highlights the need for a non-adjunctive indication. Dexcom plans on conducting outreach to all current users to inform them on when they can and cannot use CGM for treatment decisions upon approval of the new indications for use in the event that they do not receive or choose to decline one-on-one or self-training.

Based on the limitations of SMBG based-decision making and the current non-adjunctive use of CGM by patients without proper training on risks, the potential benefits of using the Dexcom G5 Mobile System in a non-adjunctive manner for diabetes management far outweigh the low residual risk.

10 PROPOSED POST-MARKETING REGISTRY STUDY

After discussions with FDA, it was determined that it would be difficult to appropriately size a premarket clinical study to capture the potential new risks associated with the indication change, given that these risks (such as severe hypoglycemia) are rare in the confines of a clinical trial and occur at a low frequency in the normal diabetic population. The Dexcom G5 Mobile System is commercially available, and the safety and effectiveness of current use has been established through clinical studies and post-market surveillance. FDA indicated that the Dexcom G5 Mobile System may have adequate accuracy, as demonstrated by the adjunctive clinical studies, to be used in a non-adjunctive setting, if the benefits should outweigh the risks of such an indication. Thus, it was mutually decided to assess the risks with simulations and human factors testing and perform a post-market study.

This decision aligns with the April 15, 2015 FDA guidance entitled "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval." In the guidance, "FDA may consider it acceptable to collect certain data in the post-market setting, rather than premarket under certain circumstances when FDA has uncertainty regarding certain benefits or risks of the device, but the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of the device at the time of premarket approval."

11 BENEFIT RISK CONCLUSION

Despite increased use of insulin pumps and improvements in insulin preparations, management of diabetes continues to present significant challenges. Non-severe hypoglycemic events occur commonly and with significant deleterious consequences to patients (Graveling and Frier, 2010) and families. Many patients continue to have severe hypoglycemic events resulting in seizures or loss of consciousness with many requiring costly emergency interventions. Most patients do not have adequate glucose control, with only 30% or fewer attaining their recommended HbA1c goals (Miller et al 2015). Although CGM is a relatively recent clinical development, it has had a profound impact on the management of diabetes (Pickup et al, 2015). The accuracy of CGM devices has greatly improved over the past decade (Bailey et al, 2014; Christiansen et al, 2013; Damiano et al, 2014), and the added benefits of trend information and hypoglycemia alerts improve diabetes management and glucose control (Chamberlain et al 2015; Pettus et al 2015). Despite the benefits of CGM, it is currently only used by approximately 16% of patients in the T1D exchange, a large registry of over 80 clinical practices from leading diabetes centers across the United States. The ongoing need for fingersticks for diabetes management undermines confidence in the CGM system and remains a barrier for patients, clinicians, and some payers, such as Centers for Medicare & Medicaid Services. A non-adjunctive indication would expand access to CGM and demand for CGM. Greater CGM use should result in an improved public health benefit, with improved care and outcomes for broader populations of insulin-using patients.

A review of the literature suggests that many patients using CGM are already using CMG in a non-adjunctive manner; however, there are currently no instructions on when and how to use CGM non-adjunctively. Modifying the Dexcom G5 Mobile System indication for non-adjunctive use will allow Dexcom to educate and train patients and clinicians on how and when to appropriately use the device without SMBG confirmation. More importantly, training will be provided about when not to base decisions on CGM data, such as when sensor glucose readings are discordant with symptoms or expectations.

Dexcom assessed the probable benefits and risks of using the Dexcom G5 Mobile System as a non-adjunctive device in accordance with the FDA Guidance for Industry titled “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,” issued March 28, 2012. Dexcom made the benefit/risk determination by considering the potential benefits of using CGM for managing diabetes as well as the probable risks introduced to the patient population. Dexcom also considered additional factors including patient tolerance for risk and availability of alternative treatments or diagnostics.

Dexcom conducted a formal risk analysis, conducted a literature review, reviewed existing clinical performance and usability data, conducted a usability study to evaluate the effectiveness of the training materials and IFU to mitigate risk, performed simulation analyses for many scenarios to compare risk between CGM- and SMBG-based decision-making for meal-insulin dosing, and performed a two-week non-adjunctive use simulated study to validate the safety and effectiveness of CGM based-decisions

relative to SMBG based-decisions. These simulations looked at virtual patient populations, much larger than could reasonably participate in clinical studies, and included a large array of physiological characteristics and patient behaviors. Similar to the confines of a clinical study, these diverse patients followed defined treatment parameters, such as how to determine an insulin dose or manage hypoglycemia. These simulations were able to stress the glucose measurement devices by testing conditions with high risks of hypoglycemia and in high risk populations, such as patients with impaired hypoglycemia awareness.

The simulations enabled clear separation between non-adjunctive CGM use and SMBG-based decisions and allowed Dexcom to compare decisions based on CGM data with decisions based on SMBG measurements simultaneously on the same virtual patient in parallel, eliminating potential physiological differences that could occur between cohorts or in behavioral changes that could occur over time in clinical studies. The simulations did identify some situations that may pose increased risk, such as on Day 1 of CGM use for a small subset of the studied population, with egregious errors in insulin adjustments based on the rate of glucose change, or with inadequate calibration. However, in nearly all of the conditions investigated in the simulations, CGM-based treatment decisions led to equivalent or fewer unmitigated hypoglycemic events relative to SMBG based insulin dosing. The evidence of benefit was greatest in the population with impaired hypoglycemia awareness. It is worth noting that even in patients considered having normal awareness, situations commonly occur resulting in diminished awareness, such as during sleep or with distractions. CGM-based decisions may be particularly beneficial during those times. In addition, CGM demonstrated large benefits relative to SMBG when insulin doses were determined during times that glucose was falling. Overall, the simulations provide strong evidence that the benefits of basing treatment decisions on the Dexcom G5 Mobile System outweigh the risks.

With CGM, decisions are based on the CGM number, glucose trends and alerts; the number and trend can be visualized with the push of a button. With SMBG, decisions are only based on numbers, obtained infrequently and requiring a fingertip lance. The point accuracy of the CGM value has greatly improved and is approaching the accuracy of blood glucose meters. As demonstrated in the simulations, which were based on the device performance observed in our clinical studies, the accuracy is now sufficient to allow CGM to be used as the primary source of glucose information for diabetes management decisions. The real-time alerts mitigate excessive risks that might result from relative inaccuracies. The preponderance of data and analysis provide reasonable assurance that the benefits from modifying the indications for use and safety statements to allow Dexcom G5 Mobile System to be used for diabetes management decisions without requiring confirmatory blood glucose measurements outweigh residual risks.

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13 APPENDIX

13.1 BACKGROUND MATERIAL FOR MEAL DOSING SIMULATION

13.1.1 MEAL DOSING OVERVIEW

A simple Monte Carlo model was chosen for meal dosing simulations because it allowed more rapid evaluation of meal dosing risk in a wide variety of scenarios with different physiological, behavioral, and device parameters. Outcomes were quantified as frequency of post-meal glucose levels >180 mg/dL (hyperglycemia), <70 mg/dL (hypoglycemia), and hypoglycemia frequency after excluding cases in which a timely low glucose alert was provided as mitigation.

The description below provides details about how simulations were performed in the nominal scenario.

13.1.2 SIMULATION DOSE DETERMINATION

Simulations consisted of a set of 50,000 virtual subjects, each with a randomly sampled pre-meal glucose level and rate of change (ROC), insulin to carb ratio (ICR), ISF, and meal carbohydrate content (see Section 13.1.4 for distributions of each). For each subject, three pre-meal insulin doses were computed: the optimal dose, a SMBG-based dose, and a CGM-based dose. The equation used to determine each dose was based on the DirecNet Applied Treatment Algorithm (DirecNet Study Group, 2008):

$$dose = \left(\frac{gluc_{meas} - gluc_{target}}{ISF} + \frac{CHO_{est}}{ICR}\right) \cdot IAF_{est} \quad (8)$$

Here $gluc_{meas}$ is the glucose level measured by either the SMBG or CGM (mg/dL), $gluc_{target}$ is the target post-meal glucose (mg/dL), CHO_{est} is the subject's estimate of the meal carbohydrate content (g), and IAF_{est} is the estimated insulin adjustment factor (IAF), a dose adjustment based on pre-meal glucose ROC (unitless). Using this algorithm, insulin dosing is adjusted up or down by 0-30% in response to rising or falling glucose (Table 42). Doses based on SMBG did not include this adjustment.

Table 42: Insulin Adjustment Factor for Different Pre-meal Glucose Rates of Change

Measured ROC (mg/dL/min)	Trend Arrow	Insulin Adjustment Factor
ROC ≥ 3	double arrow up	1.3
2 ≤ ROC < 3	single arrow up	1.2
1 ≤ ROC < 2	45º arrow up	1.1
-1 < ROC < 1	flat arrow	1
-2 < ROC ≤ -1	45º arrow down	0.9
-3 < ROC ≤ -2	single arrow down	0.8
ROC ≤ -3	double arrow down	0.7

The optimal dose was computed using each subject's actual (error-free) pre-meal glucose state, carbohydrate amount, and insulin sensitivity values. To allow for small adjustments in optimal dose for small differences in rate of change, the optimal IAF was modeled as a continuous linear function of ROC.

13.1.3 MODEL ASSUMPTIONS AND SIMPLIFICATIONS

- The dosing simulation did not involve a physiological model. Instead, the deviation between actual and optimal insulin dose was translated into a deviation of post-meal glucose level from target glucose level, and the glucose rate of change immediately preceding the post-meal glucose levels below 70 mg/dL was assumed to be -1mg/dL/min, based on Dexcom clinical data.
- Subjects were assumed to set a CGM low glucose alert threshold at 70 mg/dL in the baseline simulation. No hyperglycemia alerts were simulated for CGM.
- There was no error in a subject's estimation of their ISF or ICR in the baseline simulation.
- Subjects determining insulin dose based on SMBG were assumed to have no knowledge of their current glucose trend, and therefore calculated an insulin dose as if their glucose rate of change was 0 mg/dL.
- Subjects basing decisions on SMBG measurements were assumed to not perform post-meal glucose tests (had no mitigation for post-meal hypoglycemia).
- Subjects did not learn from their experience.
- Subjects did not have symptoms of hypoglycemia.
- The adjustments for trend taken from published guidelines (DirecNet Study Group 2008) were assumed to be optimal, and subjects using CGM were assumed to determine their insulin dose following these guidelines in the baseline simulation.

13.1.4 SIMULATION INPUT DISTRIBUTIONS

Pre-Meal Glucose Levels

Pre-meal glucose levels were sampled from the distribution described in Table 43, with uniformly distributed glucose levels within each range. This distribution is based on the glucose distribution required for evaluating blood glucose meters based on ISO criteria and is intended to explore consequences of meal dosing across a broad range of glucose values. Values below 50 mg/dL and above 400 mg/dL were excluded since a subject would not dose less than 50 mg/dL or eat carbohydrates above 400 mg/dL.

Table 43: Percent of Pre-meal Glucose Values Falling in Each Glucose Range

Glucose Range (mg/dL)	Percent Within Range
50-80	15
80-120	25
120-200	35
200-300	15
300-400	10

Pre-meal Glucose Trend

Pre-meal glucose rates of change were sampled from a uniform distribution between -4 and +4 mg/dL/min. This distribution was chosen to generate a sufficient number of simulated subjects with extreme rates of change to evaluate the effect of these extremes on simulated outcomes.

Carbohydrate Content

Meal carbohydrate content was uniformly distributed between 30 and 100 grams, typical amounts for meals in the US. The glycemic impact of other nutrients was not considered in the simulations.

Insulin Sensitivity Factors

The subject's ISF was sampled from a normal distribution with a mean of 50 mg/dL/IU and a standard deviation of 10 mg/dL/IU. Values below 20 mg/dL/IU, suggesting profound insulin resistance, were excluded. The insulin to carbohydrate ratio in grams/IU of each subject was fixed at 0.25 times the subject's ISF (Davidson et al, 2008). The insulin sensitivity of each subject was assumed to be stable for the duration of the simulation (~2-3 hours).

13.1.5 ERROR MODELS FOR CARBOHYDRATE COUNTING, SMBG AND CGM

Carbohydrate estimates used in the determination of CGM and SMBG-based insulin doses were generated assuming a normally-distributed estimation error with a coefficient of variation of 25%, based on the reported mean absolute carbohydrate counting error of 20.9% (Brazeau et al, 2013).

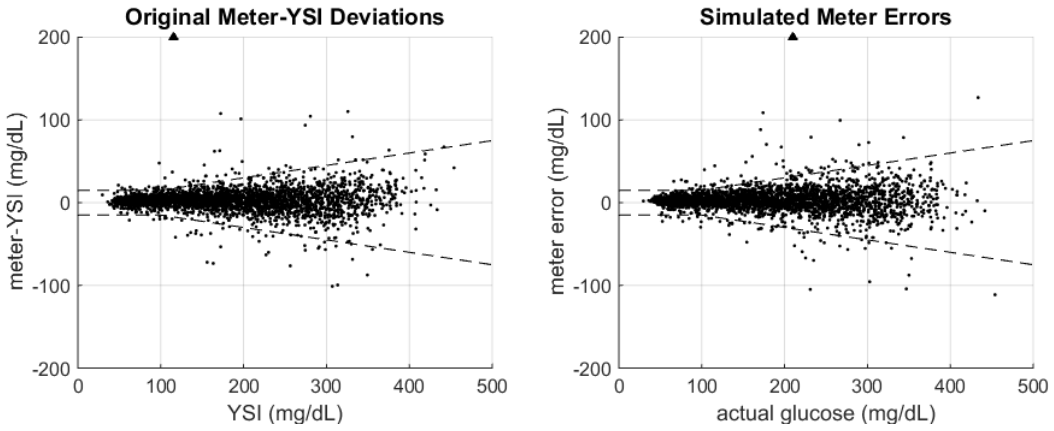
Both the SMBG and CGM error models were derived from four external Dexcom clinical studies (subjects age 3-85 with T1D or insulin-requiring T2D), with glucose tracking at ~15 minute intervals over a session that lasted up to 12 hours. All studies used the Bayer Contour Next meter for CGM calibration and YSI measurements for reference values.

SMBG errors were modeled as the combination of a fixed bias and a relative deviation:

$$gluc_{SMBG} = gluc_{actual}(1 + rd_i) + bias \quad (9)$$

To simulate a meter reading ($gluc_{SMBG}$), a relative deviation (rd_i) was randomly sampled from the set of temporally-matched SMBG-YSI bias-corrected relative deviations measured in the clinical trials and applied to the actual pre-meal glucose level ($gluc_{actual}$) along with the fixed bias (*bias*). The original measured meter errors and a set of simulated meter errors are shown in Figure 42. Original temporally-matched meter-YSI pairs used to generate the model are shown in the left panel, and a set of errors randomly generated by the model are shown in the right panel. Dashed lines show ±15 mg/dL error for actual glucose <100 mg/dL and ± 15% for actual glucose ≥ 100 mg/dL.

Figure 42: SMBG Error Model



Errors present in the CGM readings were simulated using a model based on retrospectively calculated sources of point and rate error from clinical data. This model included persistent biases caused by imperfect sensor calibration, sensor noise and artifacts, time lag, rate of change errors, and data gaps. CGM errors were applied to the pre-meal glucose values to simulate a CGM point and rate of change measurement (trend arrow), and to the post-meal glucose trace to simulate CGM low glucose alerts.

13.1.6 CALCULATION OF POST-MEAL GLUCOSE

The post-meal glucose was determined by comparing the insulin dose based on either SMBG or CGM measurements to the optimal insulin dose. Errors in the SMBG or CGM doses (deviations from optimal dose) were then converted to a post-meal glucose level by assuming that a dose error caused a

proportional change to the post-meal glucose level ($gluc_{post}$) relative to the target glucose ($gluc_{target}$), based on the subject's ISF:

$$gluc_{post} = gluc_{target} - ISF \cdot (dose - dose_{opt}) \quad (10)$$

Here, $gluc_{post}$ is the post-meal glucose level, $gluc_{target}$ is the virtual subject's target glucose, *ISF* is the subject's ISF, *dose* is the dose determined using simulated measurements from either CGM or SMBG, and $dose_{opt}$ is the optimal insulin dose.

SECTION 2

Software 505 Clinical Study Information in Current Dexcom G5 Mobile Labeling

Chapter 17

Everything Else G5:
Technical Information

17.1 Device Performance Characteristics

NOTE: We recommend that you review the information in this chapter with your healthcare professional to understand how well the Dexcom G5 Mobile CGM System performs.

The Dexcom G5 Mobile CGM System (the System) uses a glucose sensor to continuously measure and monitor your glucose levels. The sensor is "calibrated" using a commercially available blood glucose meter. Once calibrated, the System reports glucose readings up to every 5 minutes. The System was evaluated clinical studies in which System readings were compared to blood glucose values to assess its performance and how well the System readings compare to a laboratory test method that measures blood glucose values. Additionally, subjects performed self-monitoring blood glucose meter tests at home to assess the System performance in real use environment.

Although the performance characteristics of the System are presented in the following, there is no commonly accepted statistical approach for capturing performance of continuous glucose monitors (CGMs), such as the Dexcom G5 Mobile CGM System.

Clinical Study Overview

The System performance was evaluated in four separate prospective clinical studies. Two studies included adults, and two studies included pediatrics. In the following sections and tables, the studies will be identified as follows:

Adult Studies (18 years and older)
Original Adult Study: the Receiver included software version SW10050
Software 505 Adult Study: the Receiver included software version SW10505

Pediatric Studies (2 to 17 years)
Original Pediatric Study: the Receiver included software version SW10050
Software 505 Pediatric Study: the Receiver included software version SW10505

The Dexcom G5 Mobile CGM System incorporates the algorithm from software version SW10505 and has a new software number.

Overview of Adult Studies

The System performance for adults was evaluated in two separate prospective clinical studies: **Original Adult** Study (software SW10050) and the **Software 505 Adult** Study (software SW10505).

Differences between the studies include the number of subjects enrolled, the number of Systems worn by each participant, the SMBG meter used, and the number of clinic days each subject participated in during the study. An overview of each study is provided here.

The **Original Adult** Study enrolled 72 subjects, and the **Software 505 Adult** Study enrolled 51 subjects. All subjects had Type 1 or Type 2 diabetes mellitus, and required insulin or oral medication to manage their diabetes. In the **Original Adult** Study, 83% of subjects had Type 1 diabetes, and 17% of subjects had Type 2 diabetes. In the **Software 505 Adult** Study, 86% of subjects had Type 1 diabetes, and 14% of subjects had Type 2 diabetes. Both studies included subjects greater than 18 years of age.

Subjects in both studies used the System for seven days. In the **Original Adult** Study, thirty-six subjects each wore 2 sensors; in the **Software 505 Adult** Study, all subjects wore 1 sensor only. Throughout the 7-day wear period, the sensor was calibrated with an average of 2 fingersticks per day (approximately once every 12 hours). In the **Original Adult** Study, subjects used the LifeScan® OneTouch® Ultra®2 meter and in the **Software 505 Adult** Study, subjects used Bayer's CONTOUR® NEXT USB meter.

In the **Original Adult** Study, all subjects were evaluated in a controlled clinic environment on all three clinic days: Day 1, Day 4, and Day 7 of the 7-day wear period. In the **Software 505 Adult** Study, subjects were evaluated in one of the three clinic days so there are fewer data samples than in the **Original Adult** Study. While using the System in the clinic, subjects had their blood glucose measured every 15 minutes with a reliable laboratory method, the Yellow Springs Instrument 2300 STAT Plus™ Glucose Analyzer. This instrument is referred to as the "YSI." Readings from the System were reported every 5 minutes and paired with YSI values in order to characterize how well the System readings agreed with laboratory standard blood glucose results. The remainder of the study took place at home, and the System performance was also paired with the comparative meter results, referred to as the "SMBG."

Overview of Pediatric Studies

The System performance for children and adolescents was evaluated in two separate prospective clinical studies: the **Original Pediatric** Study (SW10050) and the **Software 505 Pediatric** Study (SW10505). Differences between the studies include the number of subjects enrolled, the number of Systems worn by each participant, the SMBG meter used, the length of time subjects were evaluated in a controlled clinic environment and whether or not subjects ages 13-17 had their glucose levels intentionally manipulated during the study. An overview of each study is provided here.

The **Original Pediatric** Study enrolled 176 subjects, with 16% of subjects younger than 6-years old, and the **Software 505 Pediatric** Study enrolled 79 subjects, with 20% of subjects younger than 6-years old. All subjects had Type 1 or Type 2 diabetes mellitus and required insulin or oral medication to manage their diabetes. In the **Original Pediatric** Study, about 99% of subjects had Type 1 diabetes and 1% had Type 2 diabetes. In the **Software 505 Pediatric** Study, all subjects had Type 1 diabetes. Sensors were inserted in either the abdomen or upper buttocks.

Subjects in all studies used the System for seven days. In the **Original Pediatric** Study, all subjects wore 2 sensors; in the **Software 505 Pediatric** Study, all subjects wore 1 sensor only. Throughout

the 7-day wear period, the sensors were calibrated with an average of 2 fingersticks per day (approximately once every 12 hours), using self-monitoring blood glucose (SMBG) meter values. The **Original Pediatric** Study used the LifeScan® OneTouch® Verio® IQ meter; the **Software 505 Pediatric** Study used Bayer's CONTOUR® NEXT USB meter.

All subjects were evaluated in a controlled clinic environment on Day 1, Day 4 or Day 7 of the 7-day wear period. While using the System in the clinic, subjects provided at least two fingerstick measurements per hour, and subjects ages 6-17 also provided venous blood for comparison to a laboratory method, the Yellow Springs Instrument 2300 STAT Plus™ Glucose Analyzer. This instrument is referred to as the "YSI." In the **Original Pediatric** Study, subjects' glucose levels were not intentionally manipulated during this study; in the **Software 505 Pediatric** Study, subjects ages 13-17 had their glucose levels intentionally manipulated during the clinic session. Readings from the System were reported every 5 minutes and paired with YSI values collected every 15 minutes in order to characterize how well the System readings agreed with laboratory standard blood glucose results. The remainder of the study took place at home, and the System performance was also paired with the comparative meter results, referred to as the "SMBG."

Table 1-A. System Agreement to YSI within CGM Glucose Ranges (Adult)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-YSI	Percent Within 15/15% YSI	Percent Within 20/20% YSI	Percent Within 30/30% YSI	Percent Greater than 40/40% YSI
Overall	Original	9152	71%	82%	92%	3%
	Software 505	2263	86%	93%	98%	1%
40-60	Original	512	67%	78%	88%	6%
	Software 505	120	89%	94%	98%	0%
61-80	Original	781	73%	85%	94%	2%
	Software 505	226	91%	96%	99%	0%
81-180	Original	3853	67%	78%	91%	3%
	Software 505	738	84%	92%	98%	1%
181-300	Original	2784	72%	84%	93%	4%
	Software 505	798	86%	93%	98%	1%
301-350	Original	775	82%	91%	97%	2%
	Software 505	229	86%	94%	98%	1%
351-400	Original	447	74%	84%	91%	5%
	Software 505	152	80%	92%	97%	0%

[1] *CGM readings are within 40-400 mg/dL, inclusive.*

[2] *Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Table 1-B. System Agreement to YSI within CGM Glucose Ranges (Pediatric)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-YSI	Percent Within 15/15% YSI	Percent Within 20/20% YSI	Percent Within 30/30% YSI	Percent Greater than 40/40% YSI
Overall	Original	2922	55%	68%	85%	7%
	Software 505	2262	81%	91%	96%	2%
40-60	Original	19	63%	74%	79%	21%
	Software 505	86	54%	74%	91%	3%
61-80	Original	76	61%	82%	92%	4%
	Software 505	142	77%	82%	90%	3%
81-180	Original	1155	56%	69%	84%	6%
	Software 505	805	78%	88%	97%	1%
181-300	Original	1380	55%	68%	85%	7%
	Software 505	957	89%	96%	99%	1%
301-350	Original	206	48%	62%	80%	11%
	Software 505	209	81%	91%	94%	5%
351-400	Original	86	48%	61%	79%	12%
	Software 505	63	64%	81%	83%	8%

[1]*CGM readings are within 40-400 mg/dL, inclusive.*

[2]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Agreement Relative to YSI

Agreement between the System and blood glucose values is characterized using paired System and YSI values. The System and YSI results were compared by pairing the YSI blood glucose value to a System glucose reading that occurred immediately after the YSI was collected.

The agreement of the System to blood glucose value was assessed by calculating the percentage of System readings that were within 15%, 20%, 30% and greater than 40% of the YSI values. For readings less than or equal to 80 mg/dL the absolute difference in mg/dL between the two glucose results was calculated. For values greater than 80 mg/dL the absolute percent difference (%) from the YSI values was calculated. The percentages of total readings within 15 mg/dL or 15%, 20 mg/dL

or 20%, 30 mg/dL or 30% or greater than 40 mg/dL or 40% are provided in Table 1-A and 1-B. The tables are categorized within CGM glucose ranges. When you see a CGM reading on your receiver, this table shows you how likely that reading matches your blood glucose level (measured by YSI in the study).

For example, in the **SW10505 Adult** Study (Table 1-A), the total number of data pairs considered in the analysis was 2263. Of these, 93% of the System readings fall within ± 20 mg/dL of the YSI blood glucose values ≤ 80 mg/dL and within ± 20% of YSI blood glucose values > 80 mg/dL.

Table 2-A. Number and Percentage of YSI Values When CGM Readings are "LOW" or "HIGH" (Adult)

			YSI mg/dL					Total
CGM Readings	Study[1]	CGM-YSI Pairs	< 55	< 60	< 70	< 80	≥ 80	
"LOW"	Original	n	66	84	123	142	13	155
		Cumulative Percent	42%	54%	79%	92%	8%	
	Software 505	n	11	16	17	18	0	18
		Cumulative Percent	61%	89%	94%	100%	0%	

			YSI mg/dL					Total
CGM Readings	Study[1]	CGM-YSI Pairs	> 340	> 320	> 280	> 240	≤ 240	
"HIGH"	Original	n	189	220	238	246	2	248
		Cumulative Percent	76%	89%	96%	99%	1%	
	Software 505	n	40	43	45	45	0	45
		Cumulative Percent	89%	96%	100%	100%	0%	

[1]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 2-B. Number and Percentage of YSI Values When CGM Readings are "LOW" or "HIGH" (Pediatric)

CGM Readings	Study[1]	CGM-YSI Pairs	YSI mg/dL					Total
			< 55	< 60	< 70	< 80	≥ 80	
"LOW"	Original	n	0	0	0	0	13	13
		Cumulative Percent	0%	0%	0%	0%	100%	
	Software 505	n	3	5	10	15	1	16
		Cumulative Percent	19%	31%	63%	94%	6%	

CGM Readings	Study[1]	CGM-YSI Pairs	YSI mg/dL					Total
			> 340	> 320	> 280	> 240	≤ 240	
"HIGH"	Original	n	38	51	68	69	1	70
		Cumulative Percent	54%	73%	97%	99%	1%	
	Software 505	n	14	19	22	23	1	24
		Cumulative Percent	58%	79%	92%	96%	4%	

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Agreement When CGM Reads "LOW" or "HIGH"

The System reports glucose readings between 40 and 400 mg/dL. When the System determines the glucose reading is below 40 mg/dL, it displays "LOW" in the Receiver Status Box. When the Dexcom G5 Mobile System determines that the glucose level is above 400 mg/dL, it displays "HIGH" in the Receiver Status Box. Because the System does not display glucose values below 40 mg/dL or above 400 mg/dL, the comparisons to the actual blood glucose levels (as determined by the YSI analyzer) when CGM is classified as "LOW" or "HIGH" are included separately in Table 2-A and 2-B. The tables include the numbers and the cumulative percentages when YSI values were less than certain glucose levels (for "LOW"), and when YSI values were greater than certain glucose levels (for "HIGH").

For example, in the **Software 505 Adult** Study (Table 2-A), when the System displayed “LOW” (18 occasions), 100% (18 out of 18) of the YSI values were less than 80 mg/dL, and 94% (17 out of 18) of the YSI values were less than 70 mg/dL. When the System displayed “HIGH” (45 occasions), 100% (45 out of 45) of the YSI values were greater than 240 mg/dL, and 100% (45 out of 45) of the YSI values were greater than 280 mg/dL.

Table 3-A. Concurrence of CGM Readings and YSI Values (Original Adult Study)

CGM (mg/dL)	YSI (mg/dL) Row Percentage of Matched Pairs in each CGM Glucose Range											
	< 40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	> 400	Number of Paired CGM-YSI
< 40	6%	48%	37%	7%	1%	0%	0%	0%	0%	0%	0%	155
40-60	4%	49%	36%	11%	1%	0%	0%	0%	0%	0%	0%	512
61-80	0%	22%	51%	24%	1%	0%	0%	0%	0%	0%	0%	781
81-120	0%	2%	17%	66%	13%	1%	0%	0%	0%	0%	0%	1706
121-160	0%	0%	1%	25%	60%	13%	2%	0%	0%	0%	0%	1492
161-200	0%	0%	0%	2%	28%	53%	16%	2%	0%	0%	0%	1240
201- 250	0%	0%	0%	0%	3%	21%	51%	21%	3%	1%	0%	1181
251- 300	0%	0%	0%	0%	0%	4%	19%	49%	24%	3%	0%	1018
301- 350	0%	0%	0%	0%	0%	0%	3%	28%	51%	16%	1%	775
351- 400	0%	0%	0%	0%	0%	0%	3%	10%	43%	38%	7%	447
> 400	0%	0%	0%	0%	0%	0%	1%	6%	21%	57%	15%	248

Table 3-B. Concurrence of CGM Readings and YSI Values (Software 505 Adult Study)

CGM (mg/dL)	YSI (mg/dL) Row Percentage of Matched Pairs in each CGM Glucose Range											
	< 40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	> 400	Number of Paired CGM-YSI
< 40	6%	83%	11%	0%	0%	0%	0%	0%	0%	0%	0%	18
40-60	2%	74%	22%	3%	0%	0%	0%	0%	0%	0%	0%	120
61-80	0%	19%	68%	13%	0%	0%	0%	0%	0%	0%	0%	226
81-120	0%	0%	19%	72%	8%	1%	0%	0%	0%	0%	0%	347
121-160	0%	0%	0%	17%	72%	11%	0%	0%	0%	0%	0%	246
161-200	0%	0%	0%	0%	25%	59%	16%	0%	0%	0%	0%	286
201- 250	0%	0%	0%	0%	0%	16%	70%	13%	1%	0%	0%	376
251- 300	0%	0%	0%	0%	0%	2%	16%	61%	14%	7%	0%	281
301- 350	0%	0%	0%	0%	0%	0%	2%	28%	59%	10%	1%	229
351- 400	0%	0%	0%	0%	0%	0%	0%	4%	47%	45%	5%	152
> 400	0%	0%	0%	0%	0%	0%	0%	0%	20%	38%	42%	45

Table 3-C. Concurrence of CGM Readings and YSI Values (Original Pediatric Study)

CGM (mg/dL)	YSI (mg/dL) Row Percentage of Matched Pairs in each CGM Glucose Range											
	< 40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	> 400	Number of Paired CGM-YSI
< 40	0%	0%	0%	54%	31%	15%	0%	0%	0%	0%	0%	13
40-60	0%	21%	58%	16%	5%	0%	0%	0%	0%	0%	0%	19
61-80	0%	21%	45%	30%	4%	0%	0%	0%	0%	0%	0%	76
81-120	0%	1%	20%	66%	12%	1%	0%	0%	0%	0%	0%	338
121-160	0%	0%	1%	36%	54%	7%	1%	0%	0%	0%	0%	511
161-200	0%	0%	0%	4%	40%	48%	6%	1%	0%	0%	0%	596
201- 250	0%	0%	0%	1%	9%	44%	41%	5%	0%	0%	0%	658
251- 300	0%	0%	0%	0%	2%	7%	50%	36%	3%	0%	2%	432
301- 350	0%	0%	0%	0%	0%	2%	18%	59%	21%	0%	0%	206
351- 400	0%	0%	0%	0%	0%	0%	3%	28%	50%	16%	2%	86
> 400	0%	0%	0%	0%	0%	0%	1%	14%	41%	36%	7%	70

Table 3-D. Concurrence of CGM Readings and YSI Values (Software 505 Pediatric Study)

CGM (mg/dL)	YSI (mg/dL) Row Percentage of Matched Pairs in each CGM Glucose Range											
	< 40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	> 400	Number of Paired CGM-YSI
< 40	6%	25%	63%	6%	0%	0%	0%	0%	0%	0%	0%	16
40-60	0%	33%	60%	6%	1%	0%	0%	0%	0%	0%	0%	86
61-80	0%	8%	64%	26%	2%	0%	0%	0%	0%	0%	0%	142
81-120	0%	1%	15%	69%	13%	1%	1%	0%	0%	0%	0%	314
121-160	0%	0%	0%	15%	66%	18%	1%	0%	0%	0%	0%	313
161-200	0%	0%	0%	1%	18%	66%	15%	0%	0%	0%	0%	355
201- 250	0%	0%	0%	0%	1%	17%	68%	14%	0%	0%	0%	444
251- 300	0%	0%	0%	0%	0%	0%	26%	58%	16%	0%	0%	336
301- 350	0%	0%	0%	0%	0%	0%	4%	40%	46%	9%	0%	209
351- 400	0%	0%	0%	0%	0%	0%	3%	14%	62%	21%	0%	63
> 400	0%	0%	0%	0%	0%	0%	4%	13%	29%	38%	17%	24

Concurrence of System and Laboratory Reference

Table 3-A (Original Adult Study), 3-B (Software 505 Adult Study), 3-C (Original Pediatric Study) and 3-D (Software 505 Pediatric Study) are categorized by ranges of CGM glucose readings. These tables describe, for each range of CGM glucose readings, what percentage of paired YSI values were in the same glucose range (shaded) or in glucose ranges above and below the paired CGM readings. For example, based on the Software 505 Adult Study, when CGM readings are within 81 to 120 mg/dL, you can expect your blood glucose levels are within 81 to 120 mg/dL 72% of time.

Table 4-A. System Difference to YSI within CGM Glucose Ranges (Adult)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-YSI	Mean Percent Difference	Median Percent Difference	Mean Absolute Percent Difference	Median Absolute Percent Difference
Overall	Original	9152	2.9%	1.7%	13.3%	9.8%
	Software 505	2263	2.5%	2.4%	9.0%	7.0%
*40-60	Original	512	-10.0	-8.2	13.5	9.7
	Software 505	120	-3.3	-2.1	6.9	4.8
*61-80	Original	781	-2.4	-0.4	11.4	8.6
	Software 505	226	0.8	1.4	6.7	5.4
81-180	Original	3853	4.8%	3.0%	13.8%	9.8%
	Software 505	738	3.9%	4.1%	9.6%	8.2%
181-300	Original	2784	2.1%	0.0%	11.9%	9.2%
	Software 505	798	0.6%	0.4%	8.0%	6.1%
301-350	Original	775	3.8%	2.8%	9.8%	7.9%
	Software 505	229	4.1%	3.4%	8.0%	5.8%
351-400	Original	447	10.4%	7.7%	12.8%	9.1%
	Software 505	152	7.2%	6.3%	9.2%	7.2%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

**For CGM ≤ 80 mg/dL, the difference and absolute difference in mg/dL are included instead of percent differences (%).*

Table 4-B. System Difference to YSI within CGM Glucose Ranges (Pediatric)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-YSI	Mean Percent Difference	Median Percent Difference	Mean Absolute Percent Difference	Median Absolute Percent Difference
Overall	Original	2922	13.5%	11.6%	17.4%	13.5%
	Software 505	2262	1.8%	1.2%	10.4%	7.9%
*40-60	Original	19	-18.1	-9.1	19.2	9.1
	Software 505	86	-15.3	-13.2	16.1	13.2
*61-80	Original	76	-3.7	-2.3	13.4	10.6
	Software 505	142	-4.8	-1.0	11.8	7.7
81-180	Original	1155	11.9%	9.7%	17.0%	13.0%
	Software 505	805	1.9%	0.7%	10.6%	8.1%
181-300	Original	1380	14.8%	12.4%	17.4%	13.3%
	Software 505	957	2.2%	1.0%	8.1%	6.5%
301-350	Original	206	19.2%	15.9%	19.4%	15.9%
	Software 505	209	7.8%	6.5%	11.0%	7.9%
351-400	Original	86	18.5%	15.5%	19.1%	15.5%
	Software 505	63	14.9%	11.6%	15.2%	11.6%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

*[2]Both sets of study data are presented and are labeled as **Original** (SW10050) or **Software 505** (SW10505).*

**For CGM ≤ 80 mg/dL, the difference and absolute difference in mg/dL are included instead of percent differences (%).*

Accuracy Relative to YSI

Accuracy between matched pairs was also estimated by calculating the percent difference between the System reading and the YSI value. For example, if the YSI value is 100 mg/dL and the System reading is 90 mg/dL, a 10% difference between the System and the YSI is reported. The System and YSI values were compared by pairing the System reading that fell immediately after the YSI value was collected.

In the example above, the System reading is less than the YSI value, so the percent difference reading is negative. The mean percent difference is the average of all positive and negative percent differences between the two devices; it tells you if the System reads higher or lower on average than the YSI within each glucose range.

Another estimate used to show the accuracy of the System is the absolute percent difference. The absolute percent difference tells you the percent difference or "distance" between the System and YSI values, but does not tell you whether the System is reading, on average, higher or lower than the YSI laboratory standard. The mean absolute percent difference is the average "distance" (regardless if positive or negative) between System readings and YSI values.

Accuracy measures in differences for both the **Original Adult** and **Software 505 Adult** Studies are summarized in Table 4-A. Accuracy measures in differences for both the **Original Pediatric** and **Software 505 Pediatric** Studies are summarized in Table 4-B. Table 4-A and 4-B are categorized within CGM glucose ranges.

For example, in the **Software 505 Adult** Study (Table 4-A), overall, on average, the System reads 2.5% different (Mean Percent Difference) than the reference and 9.0% absolute different (Mean Absolute Difference) than the reference values. The Median Percent Difference shows that half of the time the System reads 2.4% or less than the YSI blood glucose values and the Median Absolute Percent Difference shows that half of the time the System reads about 7.0% or less than the YSI blood glucose values.

Table 5-A. Hypoglycemia Alert and Detection Rate Evaluation in Reference to YSI 15 Minutes Before and After (Adult)

Hypoglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hypoglycemia Detection Rate	Hypoglycemia Missed Detection Rate
55	Original	50%	50%	71%	29%
	Software 505	71%	29%	68%	32%
60	Original	64%	36%	75%	25%
	Software 505	85%	15%	83%	17%
70	Original	79%	21%	83%	17%
	Software 505	92%	8%	91%	9%
80	Original	87%	13%	86%	14%
	Software 505	95%	5%	90%	10%
90	Original	90%	10%	89%	11%
	Software 505	96%	4%	94%	6%

[1]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 5-B. Hypoglycemia Alert and Detection Rate Evaluation in Reference to YSI 15 Minutes Before and After (Pediatric, Ages 6-17 Years)

Hypoglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hypoglycemia Detection Rate	Hypoglycemia Missed Detection Rate
55	Original	0%	100%	0%	100%
	Software 505	22%	78%	75%	25%
60	Original	11%	89%	25%	75%
	Software 505	42%	58%	78%	23%
70	Original	47%	53%	50%	50%
	Software 505	68%	32%	75%	25%
80	Original	55%	45%	55%	45%
	Software 505	86%	14%	91%	9%
90	Original	69%	31%	62%	38%
	Software 505	90%	10%	93%	7%
100	Original	75%	25%	62%	38%
	Software 505	91%	9%	93%	7%

[1]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 5-C. Hypoglycemia Alert and Detection Rate Evaluation in Reference to SMBG 30 Minutes Before and After (Pediatric, Ages 2-5 Years)

Hypoglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hypoglycemia Detection Rate	Hypoglycemia Missed Detection Rate
55	Original	3%	97%	57%	43%
	Software 505	25%	75%	100%	0%
60	Original	11%	89%	62%	38%
	Software 505	20%	80%	100%	0%
70	Original	29%	71%	77%	23%
	Software 505	20%	80%	100%	0%
80	Original	35%	65%	85%	15%
	Software 505	61%	39%	100%	0%
90	Original	51%	49%	89%	11%
	Software 505	78%	22%	100%	0%
100	Original	64%	36%	91%	9%
	Software 505	82%	18%	100%	0%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Low and High Glucose Alerts

The ability of the System to detect high and low glucose levels is assessed by comparing System results to YSI results at low and high blood glucose levels and determining if the alert may have sounded. The System and YSI values were compared by pairing the System reading that occurred immediately after the YSI value was collected. We suggest that you ask your doctor what alert settings would be best for you.

The Low Glucose Alert

Estimates of how well the adjustable Low Glucose Alert performs are presented in Table 5-A, 5-B and 5-C. Table 5-A represents the hypoglycemia alert evaluation within 15 minutes of the YSI value in the adult studies. Table 5-B represents the alert evaluation within 15 minutes of the YSI value for a subset of the pediatric population—subjects age 6 to 17 years who had YSI measurements every 15 minutes.

Table 5-C represents the alert evaluation within 30 minutes of an SMBG reading for 2- to 5-year old subjects in the pediatric studies.

Hypoglycemia Alert Rate

The Alert Rate shows how often the alert is right or wrong. The True Alert Rate is the % of time the device alarmed when the blood glucose level was at or below the alert setting within 15 or 30 minutes before or after the device alarmed. The False Alert Rate is the % of time the device alarmed when the blood glucose level was above the alert setting within 15 or 30 minutes before or after the device alarmed.

For example, if you set the Low Glucose Alert to 70 mg/dL and your alarm sounds, how often can you expect your blood sugar to actually be low? In the **Software 505 Adult** Study (Table 5-A), when your alarm sounds, you can expect your blood sugar to be below 70 mg/dL approximately 92% of the time and above 70 mg/dL approximately 8% of the time within the 15 minute period before or after your alarm sounds.

Hypoglycemia Detection Rate

The Detection Rate shows how often the device recognizes and alerts you to an episode of hypoglycemia or how often it misses such an event. The Hypoglycemia Detection Rate is the % of time the blood glucose level was at or below the alert setting and device alarmed within 15 or 30 minutes before or after the blood glucose was at or below the alert settings. The Hypoglycemia Missed Detection Rate is the % of time the blood glucose was at or below the alert setting, but the device did not alarm within 15 or 30 minutes before or after the blood glucose was at or below the alert setting.

For example, if you set the Low Glucose alert to 70 mg/dL, how often will your alarm alert you if your blood glucose goes below 70 mg/dL? In the **Software 505 Adult** Study (Table 5-A), when your blood sugar goes below 70 mg/dL, you can expect your alarm to sound 91% of the time and not to sound approximately 9% of time within the 15 minute period before or after your blood sugar goes below 70 mg/dL.

Table 6-A. Hyperglycemia Alert and Detection Rate Evaluation in Reference to YSI 15 Minutes Before and After (Adult)

Hyperglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hyperglycemia Detection Rate	Hyperglycemia Missed Detection Rate
120	Original	95%	5%	98%	2%
	Software 505	98%	2%	100%	0%
140	Original	94%	6%	97%	3%
	Software 505	97%	3%	99%	1%
180	Original	92%	8%	97%	3%
	Software 505	97%	3%	99%	1%
200	Original	92%	8%	97%	3%
	Software 505	96%	4%	98%	2%
220	Original	91%	9%	95%	5%
	Software 505	94%	6%	98%	2%
240	Original	91%	9%	94%	6%
	Software 505	93%	7%	95%	5%
300	Original	82%	18%	86%	14%
	Software 505	86%	14%	90%	10%

[1]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 6-B. Hyperglycemia Alert and Detection Rate Evaluation in Reference to YSI 15 Minutes Before and After (Pediatric, Ages 6-17 Years)

Hyperglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hyperglycemia Detection Rate	Hyperglycemia Missed Detection Rate
120	Original	91%	9%	98%	2%
	Software 505	98%	2%	99%	1%
140	Original	87%	13%	99%	1%
	Software 505	97%	3%	98%	2%
180	Original	75%	25%	99%	1%
	Software 505	94%	6%	98%	2%
200	Original	71%	29%	98%	2%
	Software 505	94%	6%	97%	3%
220	Original	67%	33%	97%	3%
	Software 505	93%	7%	96%	4%
240	Original	62%	38%	96%	4%
	Software 505	88%	12%	94%	6%
300	Original	43%	57%	93%	7%
	Software 505	69%	31%	84%	16%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Table 6-C. Hyperglycemia Alert and Detection Rate Evaluation in Reference to SMBG 30 Minutes Before and After (Pediatric, Ages 2-5 Years)

Hyperglycemia Alert Level (mg/dL)	Study[1]	True Alert Rate	False Alert Rate	Hyperglycemia Detection Rate	Hyperglycemia Missed Detection Rate
120	Original	92%	8%	98%	2%
	Software 505	97%	3%	99%	1%
140	Original	90%	10%	98%	2%
	Software 505	98%	2%	100%	0%
180	Original	87%	13%	96%	4%
	Software 505	99%	1%	93%	7%
200	Original	85%	15%	96%	4%
	Software 505	98%	2%	93%	7%
220	Original	81%	19%	95%	5%
	Software 505	100%	0%	97%	3%
240	Original	80%	20%	95%	5%
	Software 505	99%	1%	98%	2%
300	Original	71%	29%	90%	10%
	Software 505	95%	5%	96%	4%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

The High Glucose Alert

Estimates of how well the adjustable High Glucose Alert performs are presented in Table 6-A, 6-B and 6-C. Table 6-A represents the hyperglycemia alert evaluation within 15 minutes of the YSI value in the adult studies. Table 6-B represents the alert evaluation within 15 minutes of the YSI value for a subset of the pediatric population—subjects age 6 to 17 years who had YSI measurements every 15 minutes. Table 6-C represents the alert evaluation within 30 minutes of an SMBG reading for 2- to 5-year old subjects in the pediatric studies.

Hyperglycemia Alert Rate

The Alert Rate shows how often the alert is right or wrong. The True Alert Rate is the % of time the device alarmed when the blood glucose level was at or above the alert setting within 15 or 30

minutes before or after the device alarmed. The False Alert Rate is the % of time the device alarmed when the blood glucose level was below the alert setting within 15 or 30 minutes before or after the device alarmed.

For example, if you set the High Glucose alert to 200 mg/dL and your alarm sounds, how often can you expect your blood sugar to actually be high? In the **Software 505 Adult** Study (Table 6-A), when your alarm sounds, you can expect your blood sugar to be at or above 200 mg/dL approximately 96% of the time and not be above 200 mg/dL approximately 4% of the time within the 15 minute period before or after your alarm sounds.

Hyperglycemia Detection Rate

The Detection Rate shows how often the device recognizes and alerts you to an episode of hyperglycemia or how often it misses such an event. The Hyperglycemia Detection Rate is the % of time the blood glucose level was at or above the alert setting and the device alarmed within 15 or 30 minutes before or after the blood glucose was at or above the alert settings. The Hyperglycemia Missed Detection Rate is the % of time the blood glucose was at or above the alert setting, but the device did not alarm within 15 or 30 minutes before or after the blood glucose was at or above the alert setting.

For example, if you set your High Glucose alert to 200 mg/dL, how often will your alarm alert you if your blood glucose goes at or above 200 mg/dL? In the **Software 505 Adult** Study (Table 6-A), when your blood sugar goes above 200 mg/dL, you can expect your alarm to sound 98% of the time and not to sound approximately 2% of time within the 15 minute period before or after your blood sugar goes above 200 mg/dL.

Table 7-A. Percentage of System Readings[1] within YSI Values With Data Stratified in 2-Hour Increments After Calibration (Adult)

Time from Calibration	Study[2]	Number of Paired CGM-YSI	Percent Within 15/15% YSI	Percent Within 20/20% YSI	Percent Within 30/30% YSI	Percent Greater than 40/40% YSI
0-2 hours	Original	1929	78%	88%	96%	2%
	Software 505	469	93%	97%	99%	0%
2-4 hours	Original	1516	69%	81%	91%	4%
	Software 505	389	90%	97%	99%	0%
4-6 hours	Original	1547	69%	79%	91%	5%
	Software 505	383	85%	91%	97%	2%
6-8 hours	Original	1520	68%	79%	92%	3%
	Software 505	380	79%	90%	97%	2%
8-10 hours	Original	1555	71%	82%	92%	4%
	Software 505	347	83%	92%	98%	0%
10-12 hours	Original	1068	65%	77%	91%	4%
	Software 505	295	80%	90%	98%	0%
12-14 hours	Original	17	65%	76%	82%	12%
	Software 505	0	--	--	--	--

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 7-B. Percentage of System Readings[1] within YSI Values with Data Stratified in 2-Hour Increments after Calibration (Pediatric)

Time from Calibration	Study[2]	Number of paired CGM-YSI	Percent within 15/15% YSI	Percent within 20/20% YSI	Percent within 30/30% YSI	Percent greater than 40/40% YSI
0-2 hours	Original	648	65%	75%	87%	7%
	Software 505	545	83%	91%	97%	1%
2-4 hours	Original	649	51%	67%	86%	7%
	Software 505	460	72%	89%	96%	2%
4-6 hours	Original	630	51%	61%	80%	10%
	Software 505	428	77%	88%	95%	2%
6-8 hours	Original	409	52%	68%	85%	5%
	Software 505	325	88%	92%	94%	3%
8-10 hours	Original	296	53%	69%	84%	7%
	Software 505	305	86%	93%	97%	1%
10-12 hours	Original	253	58%	74%	89%	5%
	Software 505	198	89%	94%	98%	0%
12-14 hours	Original	37	32%	38%	65%	22%
	Software 505	1	100%	100%	100%	100%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Calibration Stability

The System must be calibrated every 12 hours. To demonstrate performance of the System over a 12-hour calibration period, Systems were evaluated to verify that performance remains consistent over the 12-hour calibration period. Systems were evaluated in 2-hour increments after calibration. Performance was estimated at each 2-hour interval and stratified by glucose values by calculating the percentage of System readings within 15 mg/dL or 15%, 20 mg/dL or 20%, 30 mg/dL or 30%, 40 mg/dL or 40% and greater than 40 mg/dL or 40% of the YSI values in Table 7-A and 7-B.

Table 8-A. Sensor Stability Relative to YSI (Accuracy Over Time[1]) - (Adult)

Day of Wear	Study[2]	Number of Paired CGM-YSI	Mean Absolute Percent Differences	Median Absolute Percent Differences	Percent Within 15/15% YSI	Percent Within 20/20% YSI	Percent Within 30/30% YSI	Percent Greater than 40/40% YSI
Day 1	Original	3023	16.7%	13.2%	59%	71%	86%	6%
	Software 505	680	10.7%	7.9%	77%	84%	96%	2%
Day 4	Original	3108	11.4%	8.2%	77%	87%	95%	2%
	Software 505	777	8.0%	6.4%	89%	96%	99%	0%
Day 7	Original	3021	11.9%	8.9%	76%	87%	95%	2%
	Software 505	806	8.5%	7.2%	90%	97%	99%	0%

[1] *CGM readings are within 40 to 400 mg/dL, inclusive.*

[2] *Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Table 8-B. Sensor Stability Relative to YSI (Accuracy Over Time[1]) - (Pediatric, Ages 6-17 Years)

Day of Wear	Study[2]	Number of Paired CGM-YSI	Mean Absolute Percent Differences	Median Absolute Percent Differences	Percent Within 15/15% YSI	Percent Within 20/20% YSI	Percent Within 30/30% YSI	Percent Greater than 40/40% YSI
Day 1	Original	1016	21.2%	15.8%	48%	61%	78%	15%
	Software 505	740	12.7%	8.5%	75%	83%	91%	4%
Day 4	Original	810	16.0%	13.9%	52%	66%	87%	3%
	Software 505	795	8.1%	6.7%	89%	97%	100%	0%
Day 7	Original	1096	15.1%	11.3%	63%	76%	89%	4%
	Software 505	727	10.4%	8.4%	80%	91%	98%	1%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 8-C. Sensor Stability Relative to SMBG (Accuracy Over Time[1]) - (Pediatric, Ages 2-17 Years)

Day of Wear	Study[2]	Number of Paired CGM-SMBG	Mean Absolute Percent Differences	Median Absolute Percent Differences	Percent Within 15/15% SMBG	Percent Within 20/20% SMBG	Percent Within 30/30% SMBG	Percent Greater than 40/40% SMBG
Day 1	Original	3216	18.8%	14.2%	53%	65%	81%	10%
	Software 505	893	14.8%	10.7%	64%	79%	91%	5%
Day 2	Original	2148	16.2%	12.4%	60%	74%	87%	6%
	Software 505	436	13.2%	10.4%	69%	81%	95%	3%
Day 3	Original	1977	15.2%	11.0%	63%	76%	89%	5%
	Software 505	441	13.8%	11.3%	66%	77%	91%	2%
Day 4	Original	2830	14.0%	10.9%	66%	79%	91%	4%
	Software 505	850	10.7%	8.5%	79%	91%	97%	1%
Day 5	Original	1768	15.4%	10.7%	67%	78%	90%	5%
	Software 505	374	11.4%	8.7%	74%	86%	96%	1%
Day 6	Original	1704	14.3%	9.8%	68%	79%	90%	4%
	Software 505	410	12.3%	9.2%	72%	80%	93%	2%
Day 7	Original	2675	12.4%	9.2%	72%	83%	94%	3%
	Software 505	860	11.3%	8.6%	79%	90%	96%	2%

[1] *CGM readings are within 40 to 400 mg/dL, inclusive.*

[2] *Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Sensor Stability

Relative to YSI

Sensors can be worn for up to 7 days. Performance was estimated by calculating the percentage of System readings within 15 mg/dL or 15%, 20 mg/dL or 20%, 30 mg/dL or 30% , 40 mg/dL or 40% and greater than 40 mg/dL or 40% of the YSI values at the beginning (Day 1), middle (Day 4) and end (Day 7) of the System lifecycle. The average and median of the absolute percent differences are included in Table 8-A and 8-B showing consistent accuracy and sensor stability over the 7-day life of the sensor.

Relative to SMBG (Pediatric Study)

Performance was also estimated by calculating the percentage of system readings within various percentages of the SMBG values at each day of the sensor wear period (Table 8-C). The average and median of the absolute percent differences are included in the table.

Precision of System Readings

A subset of subjects wore two Systems at the same time. This was to look at how similarly two Systems function on the same subject (sensor precision). Precision was evaluated by comparing the glucose readings from the two Systems worn on the same subject at the same time.

In the **Original Adult** Study, 36 subjects wore two Systems. Results showed that System readings from the two sensors generally agreed with each other within 9% (absolute percent difference) with a 7% coefficient of variation. In the **Original Pediatric** Study, all subjects wore two Systems. Results showed that System readings from the two sensors generally agreed with each other within 10% (absolute percent difference) with a 7% coefficient of variation. Only one System was worn in the **Software 505 Adult** and **Software 505 Pediatric** Studies so precision data was not collected.

Sensor Life

Sensors may be worn for up to 7 days (168 hours). To estimate how long a sensor will work over 7 days, all sensors worn were evaluated to determine how many days/hours of readings each sensor provided.

In the **Original Adult** Study, 108 sensors were evaluated. Ninety-four percent (94%) of the sensors lasted until Day 7 (145-168 hours). There were 6 (6%) sensors that ended early, four of which lasted more than 3 days.

In the **Software 505 Adult** Study, 51 sensors were evaluated. Ninety-eight percent (98%) of the sensors lasted until Day 7 (145-168 hours). There was 1 (2%) sensor that ended early, which lasted until day 5 of the sensor wear.

In the **Original Pediatric** Study, 351 sensors were evaluated. Eighty-five percent (85%) of the sensors lasted until Day 7 (145-168 hours).

In the **Software 505 Pediatric** Study, 77 sensors were evaluated. Ninety-four percent (94%) of the sensors lasted until Day 7 (145-168 hours).

Table 9-A. Number of Readings Provided by Each Sensor Over 7-Days (Adult)

% of Total Possible Readings Provided	Study[1]	Total Readings Provided (Min-Max)	% of Systems Providing That Number of Readings
0-25%	Original	167-491	2%
	Software 505	0	0%
26-50%	Original	719-914	4%
	Software 505	856-856	2%
51-75%	Original	1267-1267	1%
	Software 505	1253-1253	2%
76-100%	Original	1811-1992	94%
	Software 505	1497-1992	96%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Table 9-B. Number of Readings Provided by Each Sensor Over 7-Days (Pediatric)

% of Total Possible Readings Provided	Study[1]	Total Readings Provided (Min-Max)	% of Systems Providing That Number of Readings
0-25%	Original	103-427	3%
	Software 505	60-223	4%
26-50%	Original	569-954	3%
	Software 505	877-891	3%
51-75%	Original	1006-1484	9%
	Software 505	1131-1342	3%
76-100%	Original	1518-1992	86%
	Software 505	1623-1990	91%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

Table 10-A. System Readings Within Wear Days (Adult)

Statistic	Study[1]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	All Days[2]
Mean	Original	98%	98%	98%	98%	97%	99%	95%	97%
	Software 505	98%	99%	98%	98%	96%	99%	97%	98%
Median	Original	100%	100%	100%	100%	100%	100%	100%	100%
	Software 505	99%	100%	100%	100%	100%	100%	100%	100%
Standard Deviation	Original	5%	3%	9%	8%	10%	3%	11%	8%
	Software 505	3%	2%	8%	11%	15%	2%	13%	9%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

[2]*A total of 108 sensors were included with the Original Study and 51 sensors were included with the Software 505 Study.*

Table 10-B. System Readings within Wear Days (Pediatric)

Statistic	Study[1]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	All Days[2]
Mean	Original	97%	96%	96%	95%	94%	94%	92%	95%
	Software 505	96%	96%	95%	96%	93%	95%	93%	95%
Median	Original	99%	99%	99%	99%	99%	99%	98%	99%
	Software 505	99%	98%	99%	99%	97%	97%	98%	98%
Standard Deviation	Original	6%	10%	9%	12%	14%	14%	17%	12%
	Software 505	9%	6%	12%	10%	15%	7%	12%	11%

[1]*Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).*

[2]*A total of 108 sensors were included with the Original Study and 77 sensors were included with the Software 505 Study.*

Number of Readings Provided

The System is capable of providing a reading up to every 5 minutes, or up to 288 readings per day. For a variety of reasons, the System may not display a glucose reading and readings are "skipped." Table 9-A and 9-B estimate the number of readings you can expect to receive from the System over the entire 7-day period after calibration. Table 10-A and 10-B show the number of readings you can expect to receive from the System within each system wear day.

For the **Software 505 Adult** Study (SW10505), 96% of Systems provided between 1,497 and 1,992 valid glucose readings (or more than 75% of the expected number of readings) as seen in Table 9-A. Adjusted within each system wear-day, the System in the **Software 505 Adult** Study provided an average of 98% of all expected glucose readings (288) as seen in Table 10-A.

Table 11-A. System Agreement to SMBG Within CGM Glucose Ranges (Adult)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-SMBG	Percent Within 15/15% SMBG	Percent Within 20/20% SMBG	Percent Within 30/30% SMBG	Percent Greater than 40/40% SMBG
Overall	Original	7508	69%	81%	94%	2%
	Software 505	2992	77%	87%	96%	1%
40-60	Original	731	75%	84%	92%	4%
	Software 505	221	73%	80%	87%	7%
61-80	Original	968	78%	86%	95%	1%
	Software 505	336	77%	85%	95%	1%
81-180	Original	3141	65%	78%	93%	2%
	Software 505	1362	74%	85%	96%	1%
181-300	Original	1960	68%	81%	94%	3%
	Software 505	826	80%	90%	97%	1%
301-350	Original	450	77%	88%	98%	1%
	Software 505	161	83%	93%	99%	0%
351-400	Original	258	75%	85%	95%	2%
	Software 505	86	90%	93%	98%	1%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 11-B. System Agreement to SMBG Within CGM Glucose Ranges (Pediatric)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-SMBG	Percent Within 15/15% SMBG	Percent Within 20/20% SMBG	Percent Within 30/30% SMBG	Percent Greater than 40/40% SMBG
Overall	Original	16318	64%	76%	89%	5%
	Software 505	4264	73%	84%	94%	2%
40-60	Original	487	44%	55%	68%	19%
	Software 505	240	54%	71%	86%	7%
61-80	Original	1340	59%	70%	85%	7%
	Software 505	399	64%	76%	92%	2%
81-180	Original	7084	62%	74%	90%	5%
	Software 505	1650	72%	84%	95%	2%
181-300	Original	5627	69%	80%	90%	5%
	Software 505	1526	79%	89%	97%	2%
301-350	Original	1176	65%	77%	90%	4%
	Software 505	319	72%	83%	94%	2%
351-400	Original	604	58%	72%	86%	6%
	Software 505	130	69%	79%	86%	8%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

Table 12-A. System Difference to SMBG Within CGM Glucose Ranges (Adult)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-SMBG	Mean Percent Difference	Median Percent Difference	Mean Absolute Percent Difference	Median Absolute Percent Difference
Overall	Original	7508	-0.4%	-1.4%	14.0%	11.0%
	Software 505	2992	-2.6%	-2.7%	11.3%	8.6%
*40-60	Original	731	-9.3	-8.0	11.7	8.0
	Software 505	221	-10.3	-6.0	13.0	8.0
*61-80	Original	968	-1.0	1.0	10.7	8.0
	Software 505	336	-4.0	-2.0	10.1	7.0
81-180	Original	3141	1.4%	0.0%	14.2%	11.0%
	Software 505	1362	-2.6%	-3.1%	11.4%	8.9%
181-300	Original	1960	-0.7%	-2.8%	13.0%	10.3%
	Software 505	826	-1.4%	-2.0%	9.5%	7.4%
301-350	Original	450	-0.7%	-2.6%	10.5%	8.6%
	Software 505	161	-0.0%	0.0%	8.3%	6.0%
351-400	Original	258	5.0%	3.0%	11.9%	8.6%
	Software 505	86	3.9%	3.2%	8.1%	6.7%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

**For CGM ≤ 80 mg/dL, the differences in mg/dL are included instead of percent differences (%).*

Table 12-B. System Difference to SMBG Within CGM Glucose Ranges (Pediatric)

CGM Glucose Range[1] (mg/dL)	Study[2]	Number of Paired CGM-SMBG	Mean Percent Difference	Median Percent Difference	Mean Absolute Percent Difference	Median Absolute Percent Difference
Overall	Original	16318	2.2%	0.9%	15.3%	11.1%
	Software 505	4264	-0.7%	-1.1%	12.5%	9.5%
*40-60	Original	487	-22.1	-17.0	23.9	18.0
	Software 505	240	-15.9	-14.0	16.9	14.0
*61-80	Original	1340	-11.8	-8.0	17.0	11.0
	Software 505	399	-7.8	-6.0	13.7	10.0
81-180	Original	7084	1.1%	-1.0%	15.4%	11.4%
	Software 505	1650	-1.2%	-2.6%	12.1%	9.5%
181-300	Original	5627	5.7%	3.4%	13.5%	9.5%
	Software 505	1526	1.7%	0.9%	10.1%	7.7%
301-350	Original	1176	9.6%	7.2%	14.2%	10.4%
	Software 505	319	6.7%	5.9%	11.8%	8.9%
351-400	Original	604	12.7%	10.2%	16.1%	11.9%
	Software 505	130	12.0%	8.9%	15.7%	10.6%

[1]CGM readings are within 40 to 400 mg/dL, inclusive.

[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 (SW10505).

**For CGM ≤ 80 mg/dL, the differences in mg/dL are included instead of percent differences (%).*

Agreement and Accuracy Relative to SMBG

Agreement between the System and blood glucose values is also characterized using paired System and SMBG results (Table 11 to 12). The System and SMBG values were compared by pairing the comparative SMBG value to a System glucose reading that occurred immediately after the SMBG was collected. These results characterize the performance subjects expect during real-time use of the System in their daily diabetes management when comparing the System readings to their home blood glucose meter results. For readings less than or equal to 80 mg/dL, the absolute difference in mg/dL between the two glucose results was calculated. For values greater than 80 mg/dL, the absolute percent difference (%) from the SMBG values was calculated. The percentages of total readings within

15 mg/dL or 15%, 20 mg/dL or 20%, 30 mg/dL or 30%, 40 mg/dL or 40% or greater than 40 mg/dL or 40% were then calculated.

For example, if the System reads 100 mg/dL, it is between 81-180 mg/dL range and you can expect the System readings to be within 20% of the SMBG values 85% of the time for the **Software 505 Adult** Study, as seen in Table 11-A.

Overall, the System in the **Software 505 Adult** Study reads, on average, 2.6% lower (Mean Percent Difference) than SMBG values and 11.3% absolute different (Mean Absolute Percent Difference) than the SMBG values. The Median Percent Difference shows that half of the time the System reads lower in 2.7% or less than the SMBG values and the Median Absolute Percent Difference shows that half of the time the System reads about 8.6% or less different than SMBG values, as seen in Table 12-A.

Adverse Events

No serious adverse events or device-related serious adverse events occurred during the studies. Mild to moderate skin irritation, such as erythema or edema, occurred at the sensor needle insertion area or around the adhesive area. No infection, bruising, or bleeding occurred at the sensor needle insertion area or the adhesive area.

17.2 Product Specifications

User is the single use operator in the home environment.

Use of accessories, transducers and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.

Do not touch the metal connectors on the bottom of the transmitter and other open connectors on the receiver, charging cable and charger.

Sensor Product Specifications

Glucose Range	40-400 mg/dL
Sensor Life	Up to 7 days
Calibration	Commercially available blood glucose meter
Calibration Range	40-400 mg/dL
Storage Condition	Temperature: 36° F-77° F Humidity: 15%-85% RH
Sterilization	Sterile by radiation

SECTION 3

Proposed Patient Labeling and Training

Dexcom | G5® mobile

CONTINUOUS GLUCOSE MONITORING SYSTEM

Getting Started Guide

Table of Contents

Section 1

Welcome

Congratulations on making the Dexcom G5 Mobile Continuous Glucose Monitoring (CGM) System part of your life!

The Dexcom G5 Mobile CGM System (Dexcom G5) allows you to see real-time continuous sensor glucose readings every five minutes for up to seven days. These readings can help you find trends and patterns in your glucose levels, allowing you to see where your glucose levels have been, which direction they are headed, and how fast they are rising or falling.

1.1 Learning How to Learn

Knowing about the Dexcom G5 is your first step in creating a successful CGM experience. Before using it, learn about it.

You can train on the Dexcom G5 in the following ways:

1. Self train with the Dexcom G5 Mobile Tutorial
2. Train with our Dexcom Care Team
   (**1-877-339-2664**, Monday through Friday, 6 am to 5 pm PST)
3. Train with your healthcare professional using this Getting Started Guide

Before you begin and anytime you have questions, review the Dexcom G5 Mobile CGM User Guide (user guide). Your options to get the full user guide:

1. Download as an eBook or view/print in a .pdf format
   dexcom.com/guides
2. Online request form to receive a free printed copy
   dexcom.com/guides
3. Request a free copy by mail
   Using the business reply card found in the back of this guide
4. Request a free copy by phone
   1-888-738-3646 ext. 4300

Section 2

Indications for Use and Safety Statement

Indications for Use

The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) is a glucose monitoring system indicated for the management of diabetes in persons age 2 years and older. The Dexcom G5 is designed to replace fingerstick blood glucose testing for diabetes treatment decisions.

Interpretation of the Dexcom G5 results should be based on the glucose trends and several sequential readings over time. The Dexcom G5 also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.

The Dexcom G5 is intended for single patient use and requires a prescription.

Important User Information

Failure to use the Dexcom G5 and its components according to the instructions for use and all indications, contraindications, warnings, precautions, and cautions may result in you missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury. If your glucose alerts and readings from your Dexcom G5 do not match your symptoms or expectations, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions. Seek medical attention when appropriate.

Please review the product instructions before using the Dexcom G5. Indications, contraindications, warnings, precautions, cautions, and other important user information can be found in the product instructions that are included with, or accompany, the Dexcom G5. Discuss with your healthcare professional how you should use the information displayed on the Dexcom G5 to help manage your diabetes. The product instructions contain important information on troubleshooting the Dexcom G5 and on the performance characteristics of the system.

Contraindications

MRI/CT/ Diathermy

Remove the Dexcom G5 sensor, transmitter, and receiver before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment.

The Dexcom G5 has not been tested during MRI or CT scans or with diathermy treatment. The magnetic fields and heat could damage the components of the Dexcom G5, which may cause it to display inaccurate blood glucose readings or may prevent alerts.

Medications

Taking medications with acetaminophen while wearing the Dexcom G5 may inaccurately raise the glucose readings generated by the Dexcom G5. The level of inaccuracy depends on the amount of acetaminophen active in your body and is different for each person. Do not rely on continuous glucose monitoring (CGM) data produced by the Dexcom G5 if you have recently taken acetaminophen.

Warnings

Sensor Fractures

Do not ignore sensor fractures. Sensors may fracture or detach from the sensor pod on rare occasions. If a sensor breaks and no portion of it is visible above the skin, do not attempt to remove it. Seek professional medical help if you have symptoms of infection or inflammation—redness, swelling or pain—at the insertion site. If you experience a broken sensor, please report this to our Technical Support department at **1.877.339.2664** (toll free) or **1.858.200.0200**.

Do Not Use Damaged Goods

If the Dexcom G5 Receiver or Dexcom G5 Transmitter is damaged or cracked, do not use it. This could create an electrical safety hazard causing possible electrical shocks resulting in injury. In addition, a damaged or cracked Dexcom G5 Receiver or Dexcom G5 Transmitter may cause the Dexcom G5 System not to function properly.

Choking

Do not allow young children to hold the sensor or transmitter without adult supervision. The sensor and transmitter include small parts that may pose a choking hazard.

The following warnings may result in the consequence of missing severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) or making a treatment decision that results in injury:

Review Training Materials

Thoroughly review the training materials included with your Dexcom G5 before use. Incorrect use of the Dexcom G5 could lead you to misunderstand information produced by the system or might affect the system's performance.

Diabetes Treatment Decisions

If your Dexcom G5 does not display a sensor glucose reading and an arrow, or if you are getting inaccurate or inconsistent readings, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions.

Do Not Ignore Low/High Symptoms

Do not ignore symptoms of low or high glucose. If your glucose alerts and readings do not match your symptoms or expectations, you should obtain a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions or seek immediate medical attention.

Who Should Not Use

The Dexcom G5 was not evaluated or approved for the following persons:

- Pregnant women
- Persons on dialysis

Do not use the Dexcom G5 Mobile CGM System in critically ill patients. It is not known how different conditions or medications common to the critically ill population may affect performance of the system. Sensor glucose readings may be inaccurate in critically ill patients.

The Dexcom G5's accuracy has not been tested in people within these groups and the system's glucose readings may be inaccurate.

Calibrate on Schedule

Calibrate the Dexcom G5 at least once every 12 hours. The Dexcom G5 needs to be calibrated in order to provide accurate readings. Do not use the Dexcom G5

for diabetes treatment decisions unless you have followed the prompts from the device and calibrated every 12 hours after the initial calibration.

Placement

Do not insert the sensor component of the Dexcom G5 in a site other than the belly/abdomen (ages 2 years and older) or the upper buttocks (ages 2 to 17 years). The placement and insertion of the sensor component of the Dexcom G5 is not approved for other sites. If placed in other areas, the Dexcom G5 may not function properly.

Initial Calibration: Data/Alarm/Alert

Do not expect sensor glucose readings or alarms/alerts from the Dexcom G5 until after the 2-hour startup. The Dexcom G5 will NOT provide any sensor glucose readings or alarms/alerts until after the 2-hour startup ends AND you complete the startup calibration. Use fingerstick glucose values from your blood glucose meter during the 2-hour startup.

Sensor Storage

Store the sensor at temperatures between 36°F-77°F for the length of the sensor's shelf life. You may store the sensor in the refrigerator if it is within this temperature range. The sensor should not be stored in the freezer.

Storing the sensor improperly might cause the sensor glucose readings to be inaccurate.

Smart Device Settings

Your smart device's internal settings override any Dexcom G5 Mobile App setting. In addition, accessory devices (like a smart watch or other wearable smart devices) might override your smart device's Alarm, Alert, and notification settings.

To receive Alarm or Alerts you must:

1. Make sure the notifications for the Dexcom G5 Mobile App are turned on in the setting's menu of your smart device.
2. Check that the Dexcom G5 Mobile App hasn't been shut down by your smart device.
3. Turn on Bluetooth on your smart device.
4. Turn off the Do Not Disturb feature on your smart device (if available).
5. Restart the Dexcom G5 Mobile App after your smart device is restarted.
6. Set the volume on your smart device at a level you can hear.
7. Always run the app in the background; do not close the Dexcom G5 Mobile

App.

8. Make sure accessory devices do not override your smart device settings.

If the settings on your smart device are incorrect, your Dexcom G5 may not function properly.

The Dexcom G5 Alarm/Alert vibrations are not any different from other vibrating apps on your smart device. Medical device apps, like the Dexcom G5 Mobile App, do not have any special priorities over your smart device's features. You cannot determine if a vibration is a notification from your Dexcom G5 Mobile App or another app. The only way to know is to look at the screen.

Missed an Alarm or Alert?

An Alarm or Alert from the Dexcom G5 Mobile App cannot be heard through your smart device's speakers if headphones are plugged in.

Make sure you unplug your headphones when you are done using them, otherwise you might not hear an Alarm or Alert from the Dexcom G5.

Precautions

Sensor Package

Do not use the Dexcom G5 Sensor if its sterile package has been damaged or opened. Using a non-sterile sensor might cause infection.

Clean and Dry Before Using

Do not open the sensor package until you have washed your hands with soap and water, and let them dry. You may contaminate the insertion site and suffer an infection if you have dirty hands while inserting the sensor.

Do not insert the sensor until you have cleaned the skin near the insertion site with a topical antimicrobial solution, such as isopropyl alcohol, and allowed the skin to dry. Inserting into unclean skin might lead to infection. Do not insert the sensor until the cleaned area is dry so the sensor adhesive will stick better.

Reusable: Don't Throw Away

Do not discard your transmitter. It is reusable. The same transmitter is used for each session until you have reached the end of the transmitter's battery life.

The following precautions may result in the consequence of missing severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) or making a treatment decision that results in injury:

Be Accurate, Be Quick

To calibrate the system, enter the exact blood glucose value displayed on your blood glucose meter within five minutes of a carefully performed fingerstick glucose measurement.

Do not enter the Dexcom G5's sensor glucose readings for calibration. Entering incorrect blood glucose values, blood glucose values obtained more than 5 minutes before entry, or sensor glucose readings might affect sensor performance.

Treatment Decisions

Make diabetes treatment decisions based on the combination of the sensor glucose reading, trend arrow, and/or actionable alerts generated by the Dexcom G5.

Expiration Date

Do not use Dexcom G5 Sensors that are beyond their expiration date. Before inserting a sensor, confirm the expiration date that is listed on the package label in the following format: YYYY-MM-DD.

Do not use sensors that are beyond their expiration date because the sensor glucose readings might not be accurate.

Sensor Placement

Avoid using the same spot repeatedly for sensor insertion. Rotate your sensor placement sites, and do not use the same site for two sensor sessions in a row. Using the same site might cause scarring or skin irritation.

Avoid inserting the sensor in areas that are likely to be bumped, pushed, or compressed or areas of skin with scarring, tattoos, or irritation as these are not ideal sites to measure glucose. Insertion in these areas might affect sensor accuracy.

Avoid injecting insulin or placing an insulin pump infusion set within three inches of the sensor. The insulin might affect sensor performance.

Use Correct Transmitter, Receiver, and Sensor

Different generations of Dexcom continuous glucose monitoring system transmitters and receivers are not interchangeable with each other.

The Dexcom G5's transmitter and receiver are not compatible with the Dexcom G4 PLATINUM CGM System's transmitter and receiver. The Dexcom G5 will not work if you mix the transmitter and receiver from different generations.
You can use a Dexcom G4 PLATINUM Sensor with the Dexcom G5 System. Before using the sensor, make sure the sensor label says "Dexcom G5 Mobile/G4 PLATINUM Sensor" or "Dexcom G4 PLATINUM Sensor."

Communication Range

Avoid separating the transmitter and receiver by more than 20 feet. The transmission range from the transmitter to the receiver is up to 20 feet without obstruction. Wireless communication does not work well through water so the range is much less if you are in a pool, shower, etc.

Types of obstruction differ and have not been tested. If your transmitter and receiver are farther than 20 feet apart or are separated by an obstruction, they might not communicate or the communication distance may be shorter.

Setting Alarm/Alert Notifications

When using both a receiver and a smart device with your Dexcom G5, you must set your settings separately in each. If you set up one device and then use another, you might not get an Alarm or Alert.

Using an accessory device (like a smart watch) might override your smart device sounds. Alarms or Alerts might vibrate or be heard on the accessory instead of your smart device. After connecting any accessories, make sure that the smart device settings allow you to continue receiving Alarms or Alerts on the smart device.

Is it On?

If the receiver or smart device is turned off (Shut Down), it will not display sensor data, information, Alarm or Alerts generated by the Dexcom G5. Make sure the Display Devices are turned on; otherwise you won't get sensor glucose readings or Alarm or Alerts.

Keep Receiver Dry

Keep the USB port cover on the receiver closed whenever the USB cable is not attached. Do not submerge the receiver in water.

If water gets into the USB port, the receiver could become damaged and stop displaying readings or providing alerts.

No Alternative Site Testing

Do not use alternative blood glucose site testing (blood from your palm or forearm, etc.) for calibration. Alternative site blood glucose values may be different than those taken from a fingerstick blood glucose value and may not represent the timeliest blood glucose value. Use a blood glucose value taken only from a fingerstick for calibration. Using alternative site blood glucose values for calibration might affect the Dexcom G5's accuracy.

When Not To Calibrate

Do not calibrate if your blood glucose is changing at a significant rate, typically more than 2 mg/dL per minute. Do not calibrate when your receiver screen is showing the rising or falling single arrow or double arrow, which indicates that your blood glucose is rapidly rising or falling. Calibrating during rapid rise or fall of blood glucose may affect sensor accuracy.

Don't Share Your Transmitter

Do not share your transmitter with another person or use a transmitter from another person. The Dexcom G5 is a prescription-only medical device and is meant, or indicated, for individual use only.

The transmitter is tied to the sensor glucose readings. If the transmitter is used by more than one person, the glucose readings, alerts, and reports may be wrong.

Caution

U.S. law restricts the sale of the Dexcom G5 to sale by or on order of a physician.

Section 3

Risks and Benefits

3.1 Risks

There are some risks with using real-time CGM.

Not Receiving Alarm/Alerts

If you aren't getting your CGM Alarm/Alerts, you run the risk of not knowing you are having a severe low or high glucose.
Some hardware issues preventing Alarm/Alerts:

- Alert function is turned off
- Transmitter and display device is out of range
- Receiver or smart device isn't showing sensor glucose readings. For example, when there are data gaps due to being out of range or "???"
- Receiver or smart device battery is dead
- Unable to hear Alarm/Alerts or feel vibration
- App not running in the background
- Signal Loss Alert won't be heard if smart device is in Do Not Disturb

Using CGM for Treatment Decisions

If you are taking acetaminophen, you sensor glucose readings may be falsely high causing you to potentially miss a low glucose or treat a high glucose with insulin. Do not make any treatment decision based on your CGM when acetaminophen is active in your body.

In order to use CGM for your treatment decisions, you must calibrate a minimum of once every 12 hours to help keep your CGM system accurate. If you do not calibrate at this minimum frequency and make treatment decisions based on your CGM, you could not be getting the most accurate information and miss a high or low glucose.

In order to use CGM for your treatment decisions, you must have:

1. Sensor glucose reading
2. Trend Arrow

If you have symptoms of low or high glucose, but your CGM is not showing high or low glucose sensor readings, take a fingerstick blood glucose measurement with your BG meter. If you are a caregiver of someone using the G5 Mobile, watch how they act. If their symptoms don't match the CGM, take a fingerstick BG measurement.

Your BG meter is your back-up when/if your CGM is not showing a sensor glucose reading or your symptoms do not match your sensor readings. Remember to wash your hands before taking a fingerstick.

Sensor Glucose Reading Different from Your Expectations or Symptoms

The sensor glucose reading can be different than your expectations and symptoms. In this case, wash your hands and take a fingerstick blood glucose measurement with your BG meter to confirm your expectations and symptoms. If your sensor readings and BG meter values are different, you can calibrate your CGM system. Wash and dry your hands, repeat the BG measurement and if still different, recal brate.

If you're not receiving an Alarm/Alert, and not taking fingerstick BG measurements, you may be unaware of low or high glucose levels.

Sensor Insertion Risks

Inserting the sensor and wearing the adhesive patch might cause infection, bleeding, pain, or skin irritations (e.g., redness, swelling, bruising, itching, scarring or skin discoloration). The chance of this happening is low.

The Dexcom G5 uses the same sensor as the previous CGM system—the Dexcom G4 PLATINUM. The Dexcom G4 PLATINUM System clinical studies and complaint data showed slight redness and swelling occurring only in a small percentage of Dexcom's total patient population.

During Dexcom's G4 PLATINUM System's clinical study, no sensor wires broke however there is a remote chance sensor fragments could remain under your skin if the sensor breaks during normal wear. Sterile broken sensor wires don't pose a significant medical risk.

If a sensor wire breaks off or detaches and remains under your skin, contact your healthcare professional and call Dexcom's Technical Support toll free, 24/7, at **1.877.339.2664** or toll at **1.858.200.0200** within 24 hours.

3.2 Benefits

Daily habits impact your glucose levels. With the Dexcom G5, you can track how your exercise, carbs, stress levels, medication, or illness, influence your glucose levels.

Knowing Your Trends

Providing sensor glucose readings every five minutes, for up to seven days, the Dexcom G5 helps you detect trends and patterns. Trend information as well as the trend arrow reveals where your glucose is now, where your glucose is heading, and how fast it's changing. This provides you with a more complete picture of your glucose.

Making Treatment Decisions Based on Your CGM

With Dexcom G5, you can now use the sensor glucose readings to make your diabetes treatment decision (like how much insulin to take, when to treat a low glucose, etc.) when you have the key pieces of CGM information – trend arrow and sensor glucose

reading. If you are using the G5 Mobile to make treatment decisions, make sure your Alerts are on. Talk to your healthcare professional to determine your best Alert levels.

Helps in Your Diabetes Management

The Alarm/Alerts features keep you aware of your glucose levels. Alerts notify you when your glucose goes outside your target range or is rapidly falling or rising, letting you to take action before you get too low or too high. The Urgent Low Alarm lets you know when you are dangerously or urgently low, going below 55 mg/dL. By taking corrective measures, you lessen the time spent in your low/high range, while increasing time in your targeted range (Battelino, 2011). If you are using the G5 Mobile to make treatment decisions, make sure your Alerts are on.

Real-time CGM can help improve your A1C as well as improve the quality of your glucose control. If your A1C is at or below 7%, using a CGM such as the Dexcom G5, helps reduce hypoglycemia.

Lowering your A1C, increasing your time in your target range while decreasing time in low/high BG range is believed to reduce your risk of diabetes related complications (Ohkubo, 1995).

Some people perceive an increase in their quality of life and peace of mind when using real-time CGM.

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Section 4

System Overview

4.1 Components

Your Dexcom G5 is made up of the following:

1. Sensor and Applicator

- The sensor is inserted using the applicator
- Small sensor wire measures sensor glucose levels just below the skin
- Worn for up to seven days
- The sensor and applicator are disposable after use

2. Transmitter

- Placed into the sensor pod
- Wirelessly sends sensor glucose information to either your Dexcom G5 Mobile App, your receiver, or both
- Reusable during three month battery life

3. Display Device(s)

The Dexcom G5 Mobile App on your smart device* and/or your receiver can be used as your display device.

- Displays your sensor glucose readings
- Allows you to set and receive Alarm/Alerts
- Your display device and transmitter must be kept within 20 feet of each other

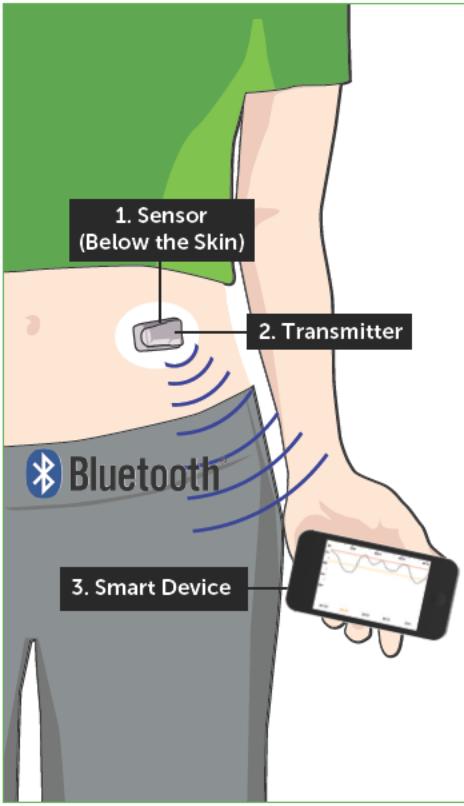
* For a list of compatible devices see: **dexcom.com/compatibility**

4.2 Choose Display Device

To set up your Dexcom G5, first choose the display device(s) you want to receive your CGM data and alerts. You have three choices, the next pages will help you make your decision.

- Your smart device only
- Your receiver only
- A combination of both

Smart Device Only

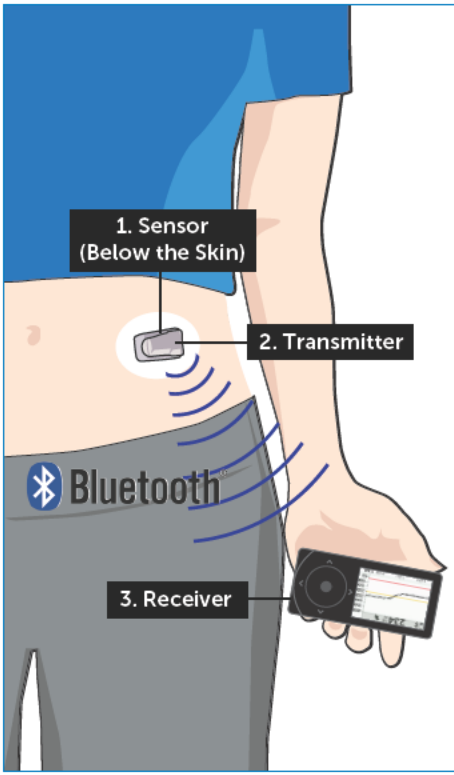


Your transmitter sends sensor glucose information directly to your smart device using *Bluetooth*® wireless technology.

Bluetooth on your smart device must be ON in order to receive CGM data and alerts.

For app setup see Section 5.

Receiver Only



Your transmitter sends sensor glucose information directly to your receiver using *Bluetooth*.

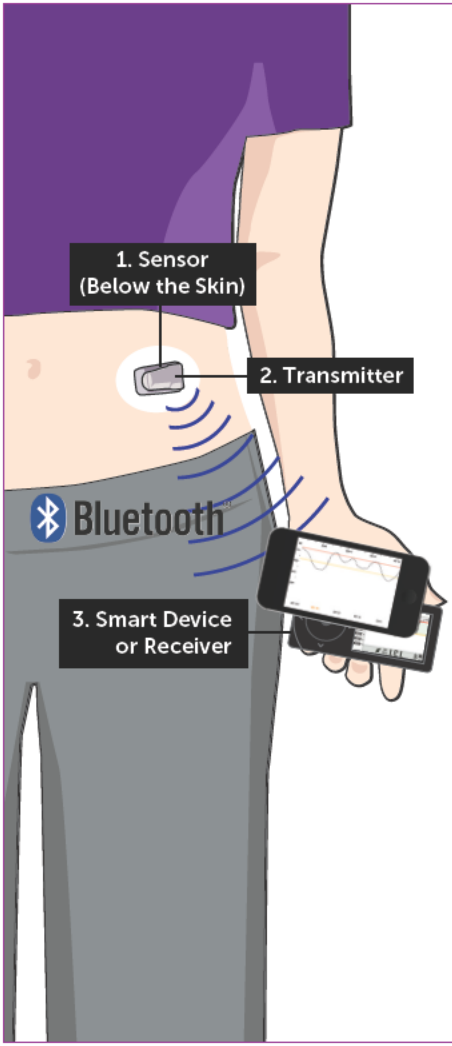
Things to consider if choosing your receiver only:

- Your receiver is a dedicated medical device
- Use when you cannot take your phone
- Battery lasts at least three days
- You will not have access to Dexcom Share*

* Dexcom Share allows you to share your sensor glucose information with Followers For more information on Dexcom Share see your user guide.

For receiver setup see Section 6.

Smart Device and Receiver



Your transmitter sends sensor glucose information directly to your app and/or your receiver, at the same time, using *Bluetooth*.

Your app and receiver do not "talk" to each other.

You can choose to use both devices at once or switch between devices.

Things to consider if choosing both devices:

- Use your app during daily activities where you already take your smart device
- Use your receiver during activities where your smart device may not be allowed (work or school)
- When you are sleeping, you can silence your smart device and use your receiver for alerts
- If you carry both devices, you will receive alerts and must acknowledge alerts on both devices

For app setup see Section 5.

For receiver setup see Section 6.

Section 5

App Setup and Operation

5.1 Install App

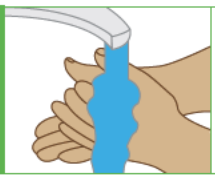
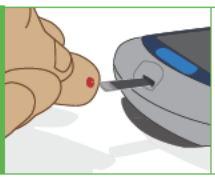
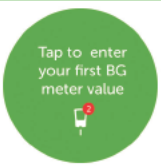
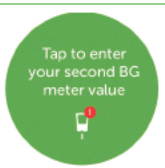
A		Install the Dexcom G5 Mobile App from your app store.
B		Log in to the app (with your existing Dexcom account) or sign up for a new account.

Once you log in, the app guides you through the setup process. This takes about 20 minutes and includes:

- Setting your high and low alerts
- Adjusting your device settings
- Entering your transmitter serial number
- Inserting your sensor and attaching your transmitter
- Pairing your transmitter with your app
- Starting your 2-hour sensor warmup

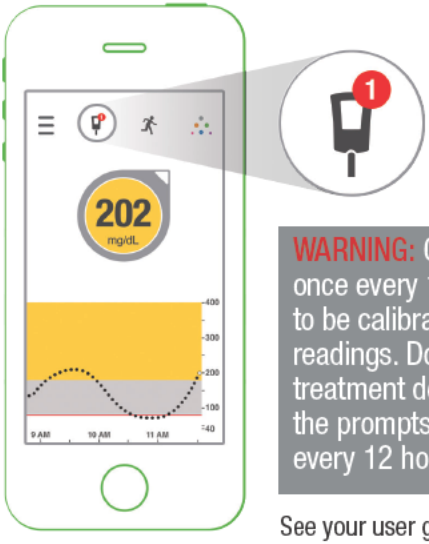
5.2 Enter Initial BG Meter Values

At the end of the 2-hour warmup, you must enter two separate BG meter values before sensor glucose readings begin.

A		Your app alerts you when you need to enter your two BG meter values. Go to your app to enter values.
B		Wash and dry your hands.
C		Take a fingerstick BG measurement using your BG meter.
D		Tap the circle to enter your BG meter value within five minutes of obtaining the value.
E		Enter the exact value from your BG meter. Tap **SAVE**.
F		Repeat steps above to enter a second BG meter value. Entering two separate BG meter values will ensure an accurate reading.

5.3 Enter BG Meter Value Every 12 Hours

BG meter values must be entered once every 12 hours at a minimum.



The meter icon shows a red badge when a BG meter value is needed.

WARNING: Calibrate the Dexcom G5 at least once every 12 hours. The Dexcom G5 needs to be calibrated in order to provide accurate readings. Do not use the Dexcom G5 for diabetes treatment decisions unless you have followed the prompts from the device and calibrated every 12 hours after the initial calibration.

See your user guide for more details.

Tips for Entering BG Meter Values

Do enter BG Meter Values:

- After washing and drying your hands
- Within 5 minutes of obtaining the value from your BG meter
- Using the exact number from your BG meter
- Using only fingerstick blood glucose values

Don't enter BG Meter Values:

- If you see a ??? (question mark), signal loss, or hourglass error on the screen
- After you have taken acetaminophen (such as Tylenol®)
- If your BG meter value is higher than 400 mg/dL or lower than 40 mg/dL.

When using both the app and the receiver at the same time, you should **enter BG meter value in only 1 device.** When you enter a value into one device, the sensor glucose values may be different on the other display device until the transmitter shares the entered value.

5.4 View Home Screen

Where You Are

To know where you are now, look at the color, and number or message.

Red = Low

Yellow = High

Gray = In Target

No Readings

LOW = Below 40 mg/dL

HIGH = Above 400 mg/dL

System Errors
Tap blue question mark for information.

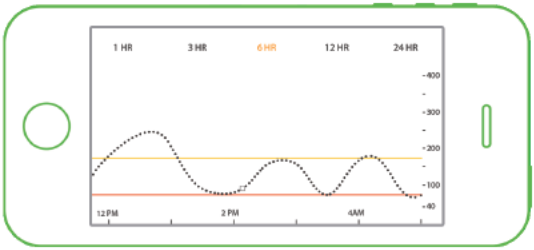
Where You Are Going

To know where you are going, look at your trend arrows. Remember it is not all about the number. Pay attention to the direction and speed of your glucose change.

	**Steady:** Glucose is steady (not increasing/decreasing more than 1 mg/dL each minute). Your glucose could increase or decrease by up to 15 mg/dL in 15 minutes.
	**Slowly rising:** Your glucose is rising 1-2 mg/dL each minute. Your glucose could increase up to 30 mg/dL in 15 minutes.
	**Rising:** Your glucose is rising 2-3 mg/dL each minute. Your glucose could increase up to 45 mg/dL in 15 minutes.
	**Rapidly rising:** Your glucose is rising more than 3 mg/dL each minute. Your glucose could increase more than 45 mg/dL in 15 minutes.
	**Slowly falling:** Your glucose is falling 1-2 mg/dL each minute. Your glucose could decrease up to 30 mg/dL in 15 minutes.
	**Falling:** Your glucose is falling 2-3 mg/dL each minute. Your glucose could decrease up to 45 mg/dL in 15 minutes.
	**Rapidly falling:** Your glucose is falling more than 3 mg/dL each minute. Your glucose could decrease more than 45 mg/dL in 15 minutes.

Where You Were

To know where you were, look at your trend graph. Turn your smart device sideways for a larger view of your trend screen.

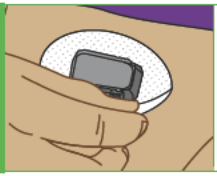


5.5 End Sensor Session

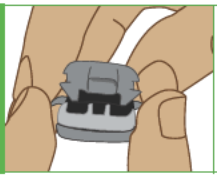
Your sensor automatically shuts off after 7 days. The app alerts you at 6 hours, 2 hours, and 30 minutes before your sensor session ends.

A	Replace sensor now. Sensor removal help Sensor insertion help	The **Replace Sensor Now** screen shows when it is time to remove your sensor.

5.6 Remove Sensor Pod and Transmitter

A		Peel the adhesive off your body like a Band-Aid®. The sensor, sensor pod and transmitter will all be removed.

NOTE: Do not remove the transmitter from the sensor pod until all components (sensor, sensor pod) are removed from your body.

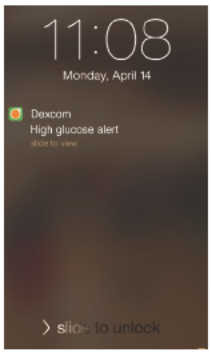
B		Use your fingers to spread the back tabs of the sensor pod. Transmitter will pop out.
C	 Keep	Keep your transmitter to use again with your next sensor.
D		Dispose of the sensor following your local guidelines for disposal of blood-contacting components.

5.7 Smart Device Settings

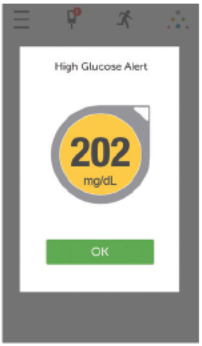
To receive CGM alerts, you must allow Dexcom to send you notifications. These notifications include CGM information only. No promotional notifications will be sent. An example of a CGM notification and an in app alert is shown below.

Example: a "High glucose alert" notification will be sent to you if your glucose rises above your high alert setting.

Sliding the notification will take you into the app.



Once in the app, tap **OK** to acknowledge the alert.



To receive alerts, make sure:

- *Bluetooth* is ON
- Your app is running in the background

If you restart you smart device, you app will not be working. You need to re-activate your app by tapping it, after restarting your smart device.

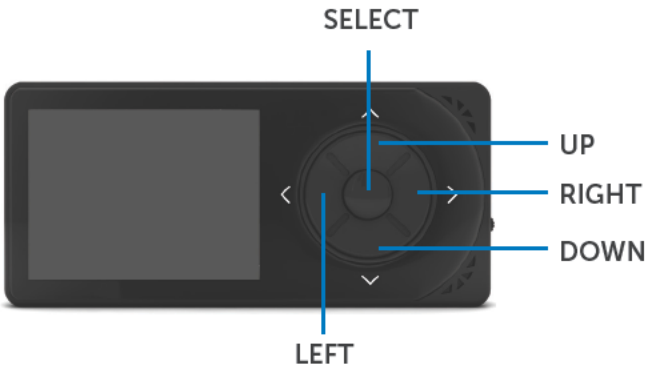
For a full list of recommended settings see your user guide.

Headphones will prevent sound from coming through the speaker. You may miss a high or low alert.

Section 6

Receiver Setup and Operation

6.1 Receiver Overview



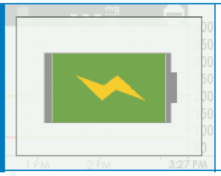
UP and DOWN: Scroll through trend screens, highlight menu items, or set values.

SELECT: Turns receiver on, selects the highlighted option, or goes to the main menu.

LEFT: Goes back to the last item or screen. This will take you back to the trend screen from the main menu.

RIGHT: Highlights the next item.

6.2 Set Up Receiver

A		Before setting up your receiver, make sure it is charged. For more information on charging see your user guide. A full charge will last about 3 days.
B		Press **SELECT** to turn your receiver on.

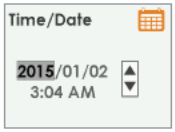
The setup wizard walks you through entering your time/date, transmitter SN, and setting up your Low/High Alerts.

Press **UP** and **DOWN** to change a value.

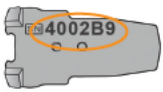
Press **RIGHT** or **SELECT** to move to the next space.

Press **SELECT** to accept changes.

C



☐ **Time/Date**
Year/Month/Day



☐ **Transmitter SN**
Your transmitter SN makes it possible for your transmitter and receiver to share your glucose information.

Your transmitter SN can be found on the back of your transmitter or on the back of your transmitter box.

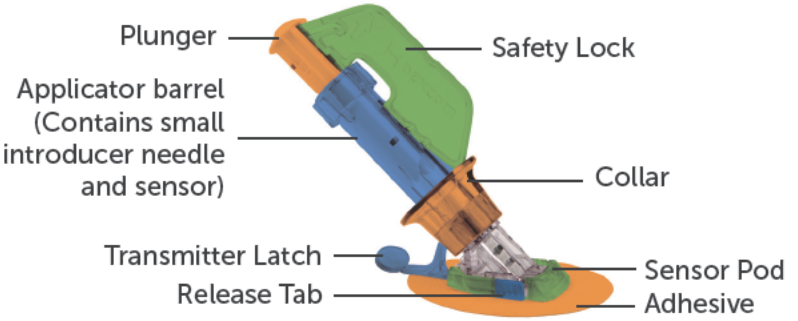
☐ **Low Alert** (Set between 60-100 mg/dL)
When your glucose is at or below your low alert setting, your device will alert you.

☐ **High Alert** (Set between 120-400 mg/dL)
When your glucose is at or above your high alert setting, your device will alert you.

The setup wizard will only start the first time you set up your receiver.

6.3 Insert Sensor

Before you begin, make sure you have alcohol wipes, a sensor, and a transmitter. Skin preparation or adhesive products (Mastisol®, Skin Tac™) are optional. Wash and dry your hands.



Choose a site at least 3 inches from your insulin pump infusion set or injection site and out of the way of your waistband. Avoid areas likely to be bumped, pushed, with scarring, tattoos or irritation.

Ages 18 years or older:
Insert in the belly

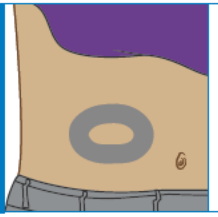
Ages 2-17 years:
Insert in the belly or the upper buttocks

A

Clean your skin at the sensor placement site with an alcohol wipe.

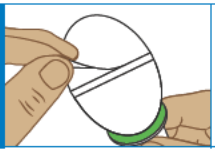
Let dry.

B



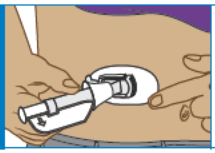
If you use an optional skin prep or adhesive product, place it on the skin in a "doughnut" shape where you will place the sensor adhesive patch. Let dry (skin may feel slightly sticky). Insert the sensor through the clean skin at the center of the doughnut where it is free of skin preparation or adhesive products.

C



Remove the adhesive backing from the sensor pod one half at a time.

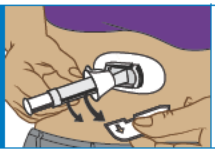
D



Place the sensor pod horizontally on your skin.

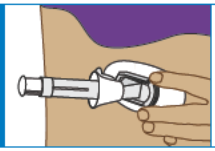
Move your fingers around the adhesive patch to secure the tape to your skin.

E



Hold the applicator, and pull the safety lock straight out.

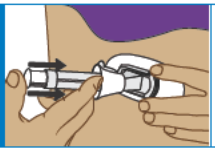
F



Place the fingers of one hand at the edge of the white adhesive.

You may pinch up on your skin using this hand.

G

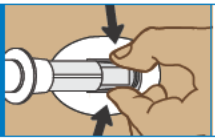


Place two fingers ABOVE the collar and your thumb on the white plunger. Push down the plunger. You should hear 2 clicks.

H

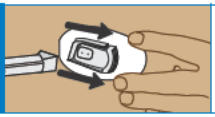
Move your two fingers from above the collar to below the collar. Pull the collar back towards your thumb until you hear 2 clicks or cannot pull back any more.

I



Squeeze the ribbed tabs on the sides of the sensor pod.

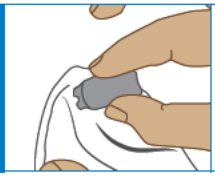
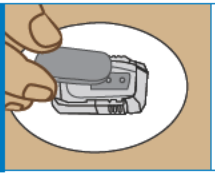
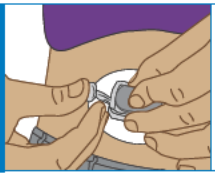
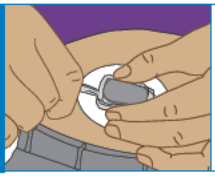
J



While **squeezing the tabs**, rock the applicator barrel forward and away from your body.

6.4 Attach Transmitter

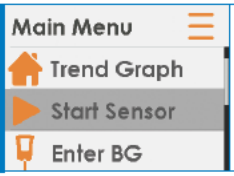
Once you have inserted the sensor, you need to attach your transmitter to the sensor pod.

A		Clean the back of your transmitter with an alcohol wipe. Let dry.
B		Place the transmitter in the sensor pod with the flat side down, and thinner side away from the transmitter latch.
C		Place one finger on the transmitter to keep it in place. With your other hand, pull the transmitter latch up and forward until you hear 2 clicks.
D		Hold the sides of your sensor pod with one hand. Remove the transmitter latch with the other hand by quickly twisting off the latch away from your body.

6.5 Start Sensor

Once you have inserted your sensor and attached your transmitter, you are ready to start your sensor.

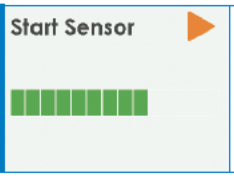
A



From any trend graph, press **SELECT** to get to the Main Menu.

Choose **Start Sensor**.

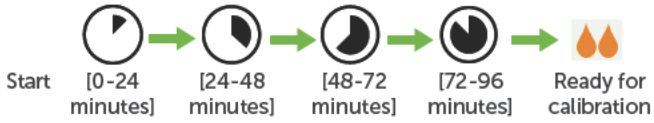
B



The **Start Sensor** screen appears on your receiver letting you know the 2-hour sensor warmup has begun.

C

A 2-hour countdown symbol will show on the receiver trend screen and will fill in during the 2-hour sensor warmup.



Keep your receiver within 20 feet during the 2-hour sensor warmup.

You will NOT receive sensor glucose readings or alerts until your 2-hour sensor warmup and two BG meter values are complete. During this time you might miss severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) events. Check with your meter during this time.

6.6 Set Up Alert Sounds

You can choose your receiver alert profiles. The sound you choose will apply to all alerts (low and high). The default alert is **Normal**. See below for an overview of the different sound options.

Vibrate: Can be used when you want to be alerted by vibration.

The fixed low alarm at 55 mg/dL will still make a sound. It will alert you by vibration first, followed by audible beeps 5 minutes later if not confirmed.

Soft: Can be used when you want your alert to be discreet.

This sets all the alerts and alarms to lower volume beeps.

Normal: This is the default and sets all the alerts and alarms to higher volume beeps.

Attentive: Can be used when you want your alert to be noticeable.

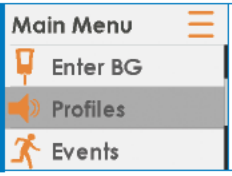
This sets all the alerts and alarms to loud with distinctive melodies.

HypoRepeat: Can be used when you want extra alerts for severe low sensor glucose readings.

This profile will keep repeating the fixed low alarm every 5 seconds until confirmed or until your reading rises above 55 mg/dL.

Follow these steps to choose your sound profile.

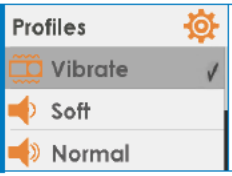
A



From any trend graph, press **SELECT** to get to the Main Menu.

Choose **Profiles**.

B

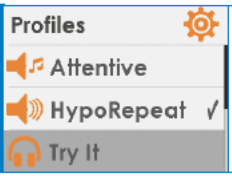


Highlight the alert profile you want to use.

Press **SELECT**.

A check mark appears to the right of the profile you choose.

C



Choose **Try It** to hear an example of your selected alert profile.

NOTE: No matter what profile you set, all alerts will notify you by vibrating first. There will be no audible beep if you confirm the alert after the first vibration.

6.7 Confirm Transmitter and Receiver are Communicating

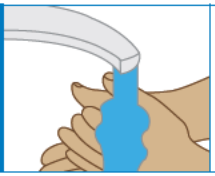
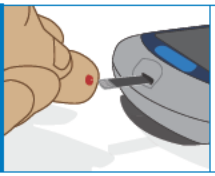
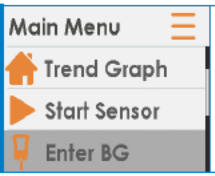
A

Check your receiver 10 minutes after attaching your transmitter to make sure your receiver and transmitter are communicating.

The *Bluetooth* symbol, in the upper left corner, blinks while looking for a transmitter and turns solid when it is found.

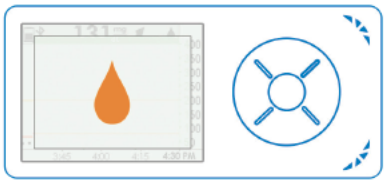
6.8 Enter Initial BG Meter Values

At the end of the 2-hour sensor warmup, you must enter two BG meter values before any sensor glucose readings will show.

A		After the 2-hour warmup, a **double blood drop prompt** will show on the receiver screen.
B		Wash and dry your hands.
C		Take a **fingerstick blood glucose measurement** using your BG meter.
D		Choose **Enter BG**. Press **SELECT**.
E		Enter the exact blood glucose value from your BG meter. Press **SELECT**. Press **SELECT** again to confirm.
F		Repeat steps above to enter a second meter value. Entering two separate BG meter values will ensure an accurate reading.

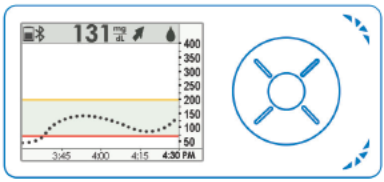
6.9 Enter BG Meter Values Every 12 Hours

BG meter values must be entered once every 12 hours at a minimum.



A single blood drop prompt will appear when a BG meter value is needed.

Press **SELECT** to confirm.



After you press **SELECT**, you will see a single blood drop in the upper right corner of the trend graph screen. Go to the **Enter BG** menu item to enter your BG meter value.

WARNING: Calibrate the Dexcom G5 at least once every 12 hours. The Dexcom G5 needs to be calibrated in order to provide accurate readings. Do not use the Dexcom G5 for diabetes treatment decisions unless you have followed the prompts from the device and calibrated every 12 hours after the initial calibration.

See your user guide for more details.

Tips for Entering BG Meter Values

Do enter BG Meter Values:

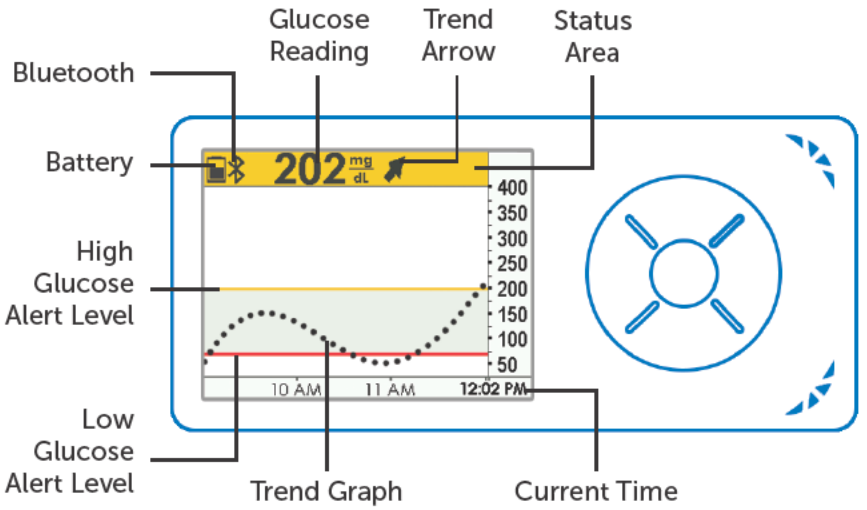
- After washing and drying your hands
- Within five minutes of testing with your meter
- Using the exact number from your meter
- Using only fingerstick blood glucose values

Don't enter BG Meter Values:

- If you see a ??? (question mark), signal loss, or hourglass error on the screen
- After you have taken acetaminophen (such as Tylenol®)
- If your BG meter value is higher than 400 mg/dL or lower than 40 mg/dL.

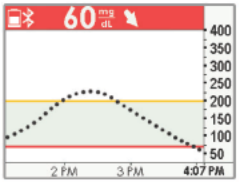
When using both the app and the receiver at the same time, you should **enter BG meter value on only 1 device.** When you enter a value into one device, the sensor glucose values may be different on the other display device until the transmitter shares the entered value.

6.10 View Receiver Trend Screen

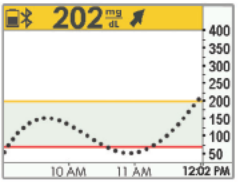


Where You Are Now

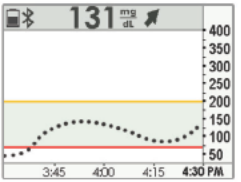
To know where you are now, look at the top bar's color and number or message



Red = Low

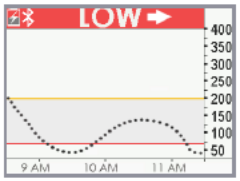


Yellow = High

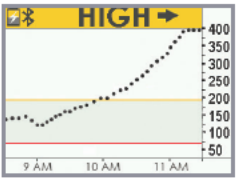


Gray = In Target

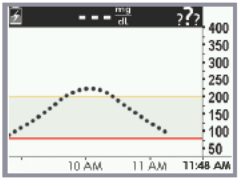
No Readings



LOW= Below 40 mg/dL



HIGH= Above 400 mg/dL



Black Bar = System Errors

See user guide for more information

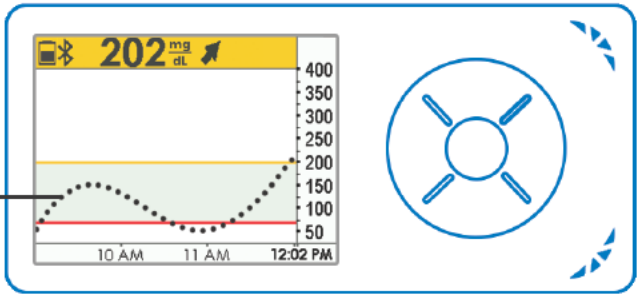
Where You Are Going

To know where you are going, look at your trend arrows. Remember it is not all about the number. Pay attention to the direction and speed of your glucose change.

→	**Steady:** Glucose is steady (not increasing/decreasing more than 1 mg/dL each minute). Your glucose could increase or decrease by up to 15 mg/dL in 15 minutes.
↗	**Slowly rising:** Your glucose is rising 1-2 mg/dL each minute. Your glucose could increase up to 30 mg/dL in 15 minutes.
↑	**Rising:** Your glucose is rising 2-3 mg/dL each minute. Your glucose could increase up to 45 mg/dL in 15 minutes.
↑↑	**Rapidly rising:** Your glucose is rising more than 3 mg/dL each minute. Your glucose could increase more than 45 mg/dL in 15 minutes.
↘	**Slowly falling:** Your glucose is falling 1-2 mg/dL each minute. Your glucose could decrease up to 30 mg/dL in 15 minutes.
↓	**Falling:** Your glucose is falling 2-3 mg/dL each minute. Your glucose could decrease up to 45 mg/dL in 15 minutes.
↓↓	**Rapidly falling:** Your glucose is falling more than 3 mg/dL each minute. Your glucose could decrease more than 45 mg/dL in 15 minutes.

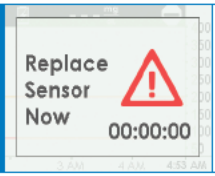
Where You Were

To know where you were, look at your trend graph.

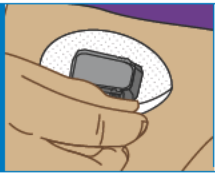


6.11 End Sensor Session

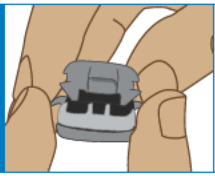
The sensor automatically shuts off after 7 days. The receiver alerts you at 6 hours, 2 hours, and 30 minutes before the sensor session ends.

A		The **Replace Sensor Now** screen shows when it is time to remove your sensor.

6.12 Remove Sensor Pod and Transmitter

A		Peel the adhesive off your body like a Band-Aid®. The sensor, sensor pod and transmitter will be removed.

NOTE: Do not remove the transmitter from the sensor pod until all components (sensor, sensor pod) are removed from your body.

B		Use your fingers to spread the back tabs of the sensor pod. The transmitter will pop out.
C	 Keep	Keep the transmitter to use again with your next sensor.
D		Dispose of the sensor following your local guidelines for disposal of blood-contacting components.

Section 7

Alarm, Alerts and Advanced Alerts

7.1 Low Glucose Alarm

The Dexcom G5 has an automatic Low Glucose alarm set at 55 mg/dL. You can't change or turn off this alarm or its re-alert settings.

7.2 Change Low/High Alerts

Part of your initial set up included setting your Low/High Alerts. You can change these settings at any time. To change your Low/High Alert go to **Menu** > **Alerts** in your app or receiver. For detailed steps see your user guide.

When using both the app and the receiver at the same time, change Alerts on each device separately.

7.3 Advanced Alerts

By default, these Alerts are turned **OFF,** but they can be turned **ON,** and customized:

Rise Rate: Your device alerts you when your glucose is rising at a rapid (2mg/dL/min) or very rapid (3mg/dL/min) rate. This feature helps you avoid staying high over a long period of time.

Fall Rate: Your device alerts you when your glucose is falling at a rapid (-2mg/dL/min) or very rapid (-3mg/dL/min) rate. This feature helps you avoid low glucose events.

By default, the following alert is turned **ON,** but can be turned **OFF,** and customized:

Signal Loss: Your device alerts you when you aren't receiving sensor glucose readings. Signal loss happens when your display device and transmitter stop communicating; make sure you are within range (20 feet), without obstruction.

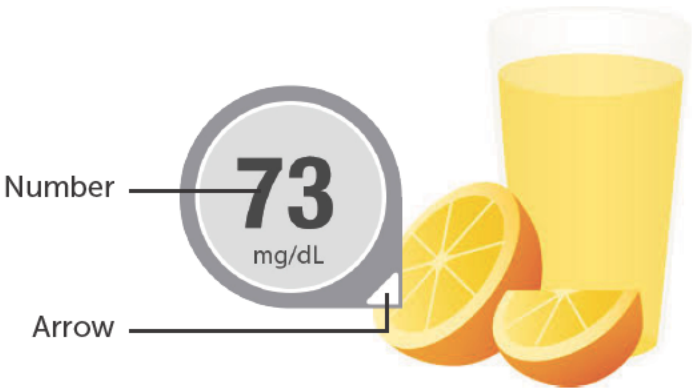
WARNING: If your Dexcom G5 does not display a sensor glucose reading and an arrow or if you are getting inaccurate or inconsistent readings, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions.

When using both the app and the receiver at the same time, you need to acknowledge alerts on each device separately.

Section 8

Using Dexcom G5 for Treatment Decisions

You are probably used to this.



Now you have another choice.

You can use your Dexcom G5 to make informed treatment decisions*.

Every person's treatment plan is different. Work with your healthcare professional (HCP) on an individualized treatment plan and to determine what Alert settings work best for you.

* Use your BG meter any time you don't have a number and arrow.

Let's look at Kim's day and how she used her Dexcom G5 to make treatment decisions:

What Kim Sees	What Kim Does and Why
Kim got a Low Alert: 	**What:** She eats an energy bar without doing a fingerstick. **Why:** An 80 mg/dL with the down arrow means her glucose is dropping. In 15 minutes, Kim could be 35 mg/dL.
Sitting down for breakfast, Kim sees: 	**What:** She doses to cover her meal. **Why:** Because of the up arrow, she takes a little more insulin. 
At lunchtime, Kim sees: 	**What:** She doses to cover her meal. **Why:** Because of the down arrow, she reduces her inslulin amount. 
For dinner Kim takes the correct amount of insulin, covering her meal. An hour later she gets a High Alert: 	**What:** She decides to **watch and wait** and not dose again. An hour later she's back in target. **Why:** Insulin takes time to work. It's important not take insulin doses too close together, or "stack" insulin. Wait at least 2 hours. You don't want to go low; sometimes it's best to **watch and wait**.

Walk through scenarios like these with your HCP.

Treatment Decision: Dexcom CGM or BG Meter

There are times when you need to rely on your meter and not your Dexcom G5.

Symptoms Don't Match

Use BG meter any time symptoms don't match sensor glucose readings. For example, you feel low, but your readings show you are in your target range. You know your body, listen to it. When in doubt, double check.

Just Took Acetaminophen

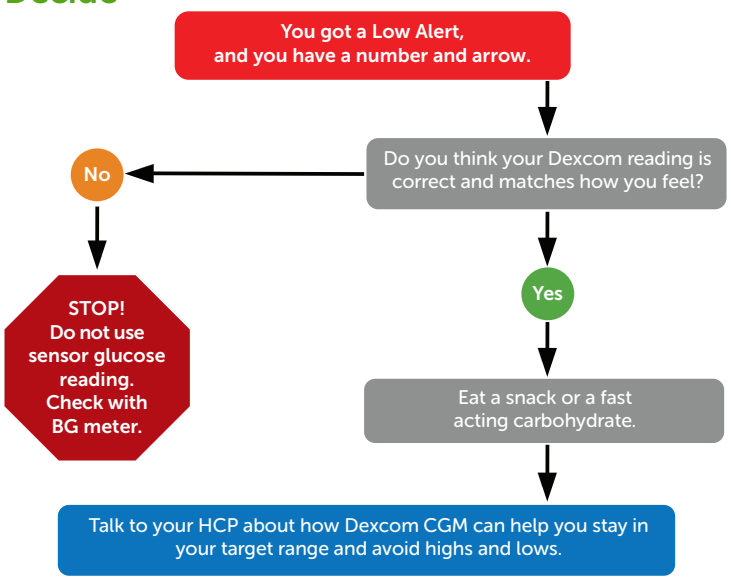
Use your BG meter if acetaminophen is in your system. Any medications containing acetaminophen, such as Tylenol, can give you a false high reading.

No Arrows or Readings

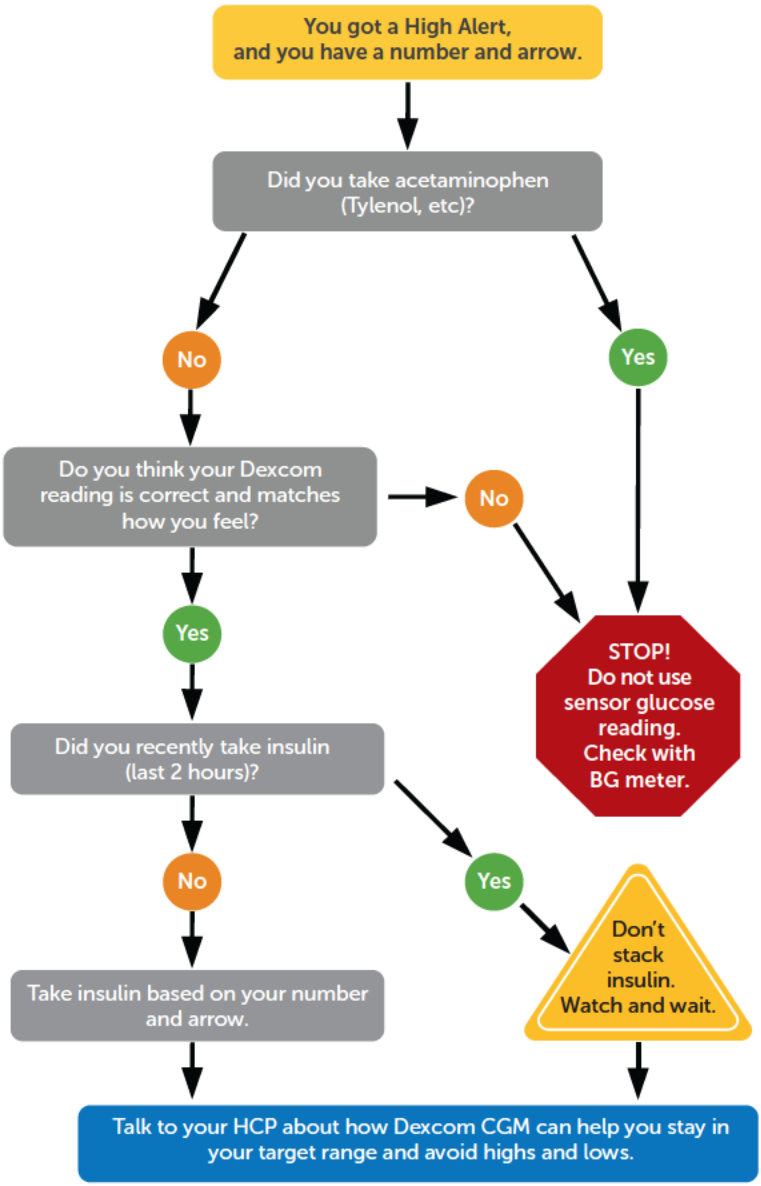
Use your BG meter any time you don't have a number and arrow on your trend screen.

No number, no arrow, no Dexcom G5 treatment decision.

You Decide



You Decide


You got a High Alert, and you have a number and arrow.
Did you take acetaminophen (Tylenol, etc)?
No
Yes
Do you think your Dexcom reading is correct and matches how you feel?
No
Yes
STOP! Do not use sensor glucose reading. Check with BG meter.
Did you recently take insulin (last 2 hours)?
No
Yes
Don't stack insulin. Watch and wait.
Take insulin based on your number and arrow.
Talk to your HCP about how Dexcom CGM can help you stay in your target range and avoid highs and lows.

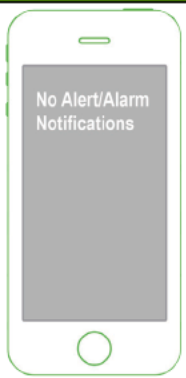
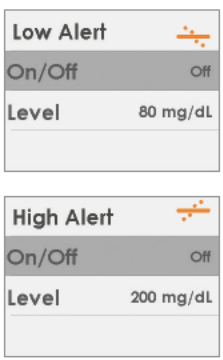
Section 9

Troubleshooting

The solutions here are meant to be brief and not all inclusive. For full troubleshooting information view the user guide at dexcom.com/guide.

In your app, tap the blue question mark for more information on any issue or error you see.

9.1 No Alarm/Alerts

Device	What you see	Problem	What you do
Smart Device		Not receiving Alerts	**Check** that smart device notifications are on. **Check** that your smart device is not on mute (if applicable). As a reminder, your Signal Loss Alert won't make a sound if your smart device's Do Not Disturb or Silent is on.
Receiver			In the receiver's main menu turn Alert to On If this continues, call Technical Support.

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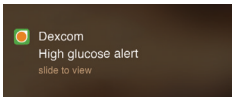
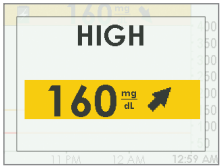
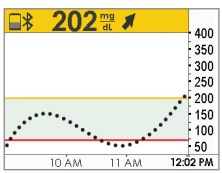
Device	What you see	Problem	What you do
Smart Device		Not hearing Alerts	**Check** that your smart device is not on mute or vibrate (if applicable). **Check** that headphones are not plugged in. As a reminder, your Signal Loss Alert won't make a sound if your smart device's Do Not Disturb or Silent is on.
Receiver			The receiver vibrates before it gives an audible alert. If you acknowledge the vibration by pressing select. You will not get an audible alert.

9.2 Sensor Glucose Readings

Device	What you see	Problem	What you do
BG Meter		Sensor readings and BG meter glucose values often don't show the same	Differences are not uncommon. Readings from different body fluids may be slightly different: **Meter** - from blood **Sensor** - from interstitial fluid **20/20 Rule** If the meter shows 80 or less, CGM should read within ± 20 points. If the meter shows 80 or above, the CGM should read ± 20%. Example: a 202 mg/dL sensor reading and a 188 mg/dL glucose meter value = a 7% difference (this is still considered accurate). In this example, the Dexcom could show up to 225 and still be considered accurate Outside of 20/20 rule: **Calibrate** again.
Smart Device			
Receiver			

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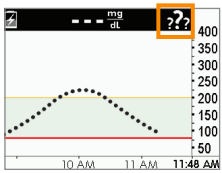
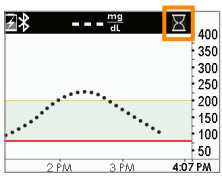
WARNING: Do not ignore symptoms of low or high glucose. If your glucose alerts and readings do not match your symptoms or expectations, you should obtain a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions or seek immediate medical attention.

(Continued from previous page)

Device	What you see	Problem	What you do
Smart Device		Not getting sensor glucose readings	**Wait** System will often resolve itself. **Check** transmitter—is it properly inserted into sensor pod? Make sure you haven't taken acetaminophen. *Don't* calibrate. If this continues for over 3 hours, call Technical Support.
Receiver			
Smart Device		Not getting sensor glucose readings	**Wait** System will often resolve itself. *Don't* calibrate. **Check** transmitter—is it properly inserted into sensor pod? Make sure you haven't taken acetaminophen. *Don't* calibrate. If this continues for over 3 hours, call Technical Support.
Receiver			

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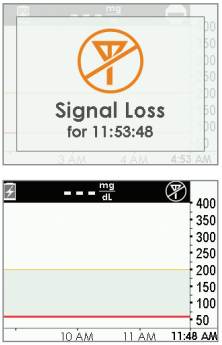
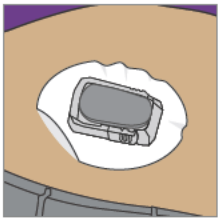
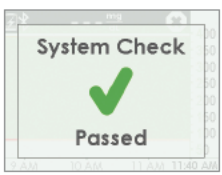
Device	What you see	Problem	What you do
Smart Device		System display device and transmitter not communicating	*Don't* calibrate. **Wait** 10 minutes. **Move** *display device* and *transmitter* within 20 feet of each other without obstruction. **Wait** another 10 minutes. **App (if not resolved):** 1. **Go** to *Settings*. 2. **Tap** *Bluetooth*. 3. **Turn** *Bluetooth Off* and *On*.
Receiver			

WARNING: If your Dexcom G5 does not display a sensor glucose reading and an arrow, or if you are getting inaccurate or inconsistent readings, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions.

9.3 Adhesive

Picture	Problem	What you do
	Sensor pod won't stick	**Use** adhesive products (Mastisol®, Skin Tac™). Make sure adhesive is not placed where the needle inserts. **Put** medical tape over sensor pod's white adhesive patch (e.g., Blenderm). **Don't** place tape over the transmitter.

9.4 Hardware Errors

Device	What you see	Problem	What you do
Receiver		Won't turn on: Battery dead	**Charge** *receiver* using electrical outlet, not computer/laptop. Full charge may take up to five hours.
Receiver		After full charge session: Won't turn on	**Reset** *receiver*: **Connect** *receiver* to *charger*. **Insert** end of paper clip into small circular hole on receiver's back. **Push down** on paper clip. Receiver will vibrate. Processing screen appears. **Charge** *receiver*.
Receiver		System Recovery	Do nothing. Receiver is able to continue to work and recover from an error. App: **Tap** *OK* to clear Alert. Receiver: **Press** *Select* to clear Alert.

9.5 Calibration Errors

<table>
<tr><th>Device</th><th>What you see</th><th>Problem</th><th>What you do</th></tr>
<tr><td>Smart Device</td><td> 
</td><td rowspan="2">System didn't accept recent calibration (see Sensor Glucose Readings troubleshooting for a possible reason)

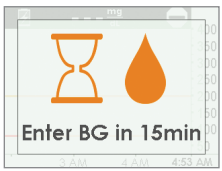
No sensor glucose readings will be displayed until error is resolved</td><td rowspan="2">Wait 15 minutes.

Enter 1 calibration.

If error screen still appears, enter 1 more BG meter value.

Wait 15 minutes.

If no sensor glucose readings appear on the display, the sensor needs to be replaced.

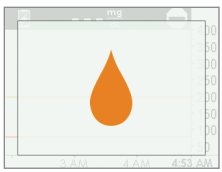
Call Technical Support to report error.</td></tr>
<tr><td>Receiver</td><td> 
</td></tr>
<tr><td>Smart Device</td><td> 
</td><td rowspan="2">System didn't accept recent calibration</td><td rowspan="2">Enter 1 BG meter value.

Wait 15 more minutes.

If error screen still appears, enter 1 more BG meter value.

Wait 15 minutes.

If no sensor glucose readings appear on the display, the sensor needs to be replaced.

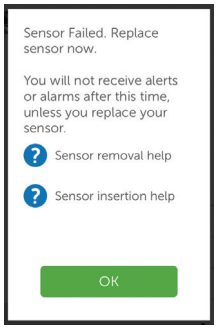
Call Technical Support to report error.</td></tr>
<tr><td>Receiver</td><td>  </td></tr>
<tr><td>BG Meter</td><td> 
</td><td>System will not accept calibration if outside of the 40-400 mg/dL range</td><td>Wait until your glucose is between 40-400 mg/dL.

Calibrate only when your BG meter values are between 40-400 mg/dL.</td></tr>
</table>

9.6 Transmitter Errors

Device	What you see	Problem	What you do
Smart Device		Transmitter not working Sensor session automatically stopped No sensor glucose readings displayed	**Call** Technical Support to report issue. **Start checking** BG value using BG meter. App: **Tap** *OK* to clear Alert. Receiver: **Press** *Select* to clear. Will not re-alert once cleared. **Order** new transmitter.
Receiver			
Smart Device		Pairing Failed	**Check** transmitter SN in display device is correct. If wrong: **Stop** *sensor session*. **Re-Enter** correct transmitter SN. App: Menu > Trans SN > **Enter** correct SN Receiver: Settings > Transmitter SN > **Enter** correct SN If correct: **Call** Technical Support.
Receiver			

9.7 Sensor Errors

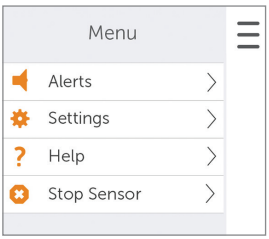
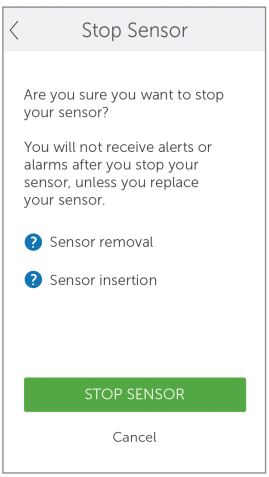
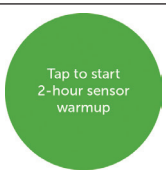
Device	What you see	Problem	What you do
Smart Device		Sensor not working	**Call** Technical Support to report issue. **Start checking** BG value using BG meter. App: **Tap** *OK* to clear Alert. Receiver: **Press** *Select* to clear. Will not re-alert once cleared. **Replace** sensor.
Receiver			

9.8 Ending Sensor Session Early

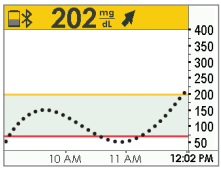
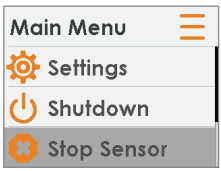
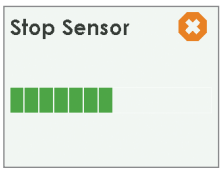
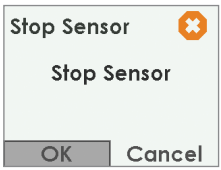
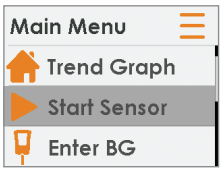
You may want to force quit a sensor session early.

While the end result is the same (ending a sensor session), the steps differ between the app and receiver. If you're using both, there is no need to stop the sensor session in each: the other display will see the session has stopped.

App: Ending Your Sensor Session Early

Step	What you see	What you do	What it means
1		**Tap** *Main Menu* icon.	Access Main Menu.
2		**Tap** *Stop Sensor*.	Ends sensor session. During session: • *Stop Sensor* option appears Not in active session: • *Start Sensor* option appears
3		**Tap** *Stop Sensor*.	Blue “?” icons provide additional information.
4		**Remove** sensor. **Insert** new sensor. **Tap** *green circle* to start new session.	Ready for new session.

Receiver: Ending a Sensor Session Early

Step	What you see	What you do	What it means
1		**Press** *Select*.	Go to Main Menu.
2		**Press** *Down Arrow* to *Stop Sensor*. **Press** *Select*.	Ends sensor session. During session, *Stop Sensor* option appears.
3		**Wait**.	Thinking screen.
4		**Press** *Select*.	Allows you to confirm stop sensor. Return to Main Menu.
5		**Remove** sensor. **Insert** new sensor. **Press** *Start Sensor* when ready for new session.	Ready to start a new session. When not in an active session *Start Sensor* option appears.

Please call the Dexcom Technical Support Team, 24/7, toll free at (b)(4) toll at 1(b)(4) if any of these errors continue and the instructions don't resolve the issue.

Section 10

Warranty

10.1 Receiver Warranty Information

Dexcom G5 Mobile CGM System's Limited Warranty

What's Covered and for How Long?

Dexcom, Inc. ("Dexcom") provides a limited warranty to the original purchaser ("you" or "Purchaser") that the Dexcom G5 Mobile Receiver (the "Receiver") is free from defects in material and workmanship under normal use ("Limited Warranty") for the period starting from the shipment date and continuing for a year following the shipment date ("Warranty Period"):

Dexcom G5 Mobile Receiver: **1 year** from shipment date

NOTE: If you received this Receiver as a replacement for an in-warranty Receiver, the Limited Warranty for the original Receiver shall continue for the Warranty Period on the original Receiver, but the replacement is not subject to any other warranty.

What's Not Covered?

This Limited Warranty is based on the Purchaser properly using the CGM system in accordance with the documentation provided by Dexcom. You are not permitted to use the CGM system otherwise. You understand that misusing the CGM system, improperly accessing it or the information it processes and transmits, "jailbreaking" your CGM system or cell phone, and taking other unauthorized actions may put you at risk, cause the CGM system to malfunction, is not permitted and voids your Limited Warranty.

This Limited Warranty does not cover:

1. Defects or damage resulting from accident, misuse, abuse, neglect, unusual physical, electrical or electromechanical stress, modification of any part of the product, or cosmetic damage.
2. Equipment with the ID number removed or made illegible.
3. All surfaces and other externally exposed parts that are scratched or damaged due to normal use.
4. Malfunctions resulting from the use of the Receiver in conjunction with accessories, ancillary products, and peripheral equipment, whether hardware or software, not furnished or approved by Dexcom.
5. Defects or damage from improper testing, operation, maintenance, installation, or adjustment.

6. Installation, maintenance, and service of products or services other than the CGM system (which may be subject to a separate limited warranty), whether provided by Dexcom or any other party; this includes your cell phone or smart device and your connection to the Internet.
7. Equipment which has been taken apart physically or which has had any of its software accessed in any unauthorized manner.
8. **Water damage to the Receiver.**
    a. **Receiver is not water resistant.**
    b. **Do not get the receiver wet at any time.**

Dexcom's Obligations Under the Limited Warranty

During the Warranty Period, Dexcom will replace, without charge to purchaser, any defective Dexcom G5 Mobile Receiver.

To return, you must send the Receiver to an authorized Dexcom Technical Support Department. Make sure you package the Receiver adequately for shipping.

The return package needs to include:

1. Receiver
2. Sales receipt or comparable substitute proof of sale showing the date of purchase
3. Receiver's Serial Number
4. Seller's name and address

Call Dexcom Technical Support Department for delivery information help:

- Toll free: (b)(4)
- Charges may apply: (b)(4)

Upon receipt, Dexcom will promptly replace the defective Receiver.

If Dexcom determines the Receiver isn't covered by this Limited Warranty, Purchaser must pay all shipping charges for the Receiver's return by Dexcom.

Limits on Dexcom's Warranty and Liability Obligations

The Limited Warranty described above is the exclusive warranty for the Receiver, and in lieu of all other warranties, expressed or implied, either in fact or by operation of law, statutory or otherwise.

Dexcom expressly excludes and disclaims all other warranties, including without limitation any warranty of merchantability, fitness for a particular purpose, or non-infringement, except to the extent prohibited by applicable law.

Dexcom shall not be liable for any special, incidental, consequential, or indirect damages, however caused, and on any theory of liability, arising in any way out of the sale, use, misuse, or inability to use, any Dexcom G5 Mobile CGM System or

any feature or service provided by Dexcom for use with the Dexcom G5 Mobile CGM System.

These limits on Dexcom's warranty and liability obligations apply even if Dexcom, or its agent, has been advised of such damages and notwithstanding any failure of essential purpose of this Limited Warranty and the limited remedy provided by Dexcom.

This Limited Warranty is only provided to the original Purchaser and can't be transferred to anyone else, and states Purchaser's exclusive remedy.

If any portion of this Limited Warranty is illegal or unenforceable by reason of any law, such partial illegality or enforceability shall not affect the enforceability of the remainder of this Limited Warranty. This Limited Warranty will be enforced to the maximum extent permitted by law.

10.2 Transmitter Warranty Information

Dexcom G5 Mobile Transmitter Limited Warranty

What's Covered and for How Long?

Dexcom, Inc. ("Dexcom") provides a limited warranty to the original purchaser that the Dexcom G5 Mobile Transmitter is free from defects in material and workmanship under normal use for the period commencing on the date of first use by the original purchaser (the "Date of First Use") and expiring three (3) months thereafter; provided, that, the Date of First use occurs within five (5) months of the date of shipment (or disbursement) of the transmitter to the original purchaser.

NOTE: If you received this Transmitter as a replacement for an in-warranty Transmitter, the Limited Warranty for the original Transmitter shall continue for the Warranty Period on the original Transmitter, but the replacement is not subject to any other warranty.

What's Not Covered?

This Limited Warranty is based on the Purchaser properly using the CGM system in a timely manner and in accordance with the documentation provided by Dexcom. You are not permitted to use the CGM system otherwise. You understand that misusing the CGM system, improperly accessing it or the information it processes and transmits, "jailbreaking" your CGM system or cell phone, and taking other unauthorized actions may put you at risk, cause the CGM system to malfunction, is not permitted and voids your Limited Warranty.

This Limited Warranty does not cover:

1. Defects or damage resulting from accident, misuse, abuse, neglect, unusual physical, electrical or electromechanical stress, modification of any part of the product, or cosmetic damage.
2. Equipment with the ID number removed or made illegible.

3. All surfaces and other externally exposed parts that are scratched or damaged due to normal use.
4. Malfunctions resulting from the use of the Transmitter in conjunction with accessories, ancillary products, and peripheral equipment, whether hardware or software, not furnished or approved by Dexcom.
5. Defects or damage from improper testing, operation, maintenance, installation, or adjustment.
6. Installation, maintenance, and service of products or services other than the CGM system (which may be subject to a separate limited warranty), whether provided by Dexcom or any other party; this includes your cell phone or smart device and your connection to the Internet.
7. Equipment which has been taken apart physically or which has had any of its software accessed in any unauthorized manner.
8. Water damage to Transmitter.
    a. Beyond specifications listed in Dexcom G5 Mobile CGM System's User Guide.
    b. User Guide is included in the Dexcom G5 Mobile System's Receiver package.
    c. Located on dexcom.com.

Dexcom's Obligations Under the Limited Warranty

During the Warranty Period, Dexcom will replace, without charge to purchaser, any defective Dexcom G5 Mobile Transmitter.

To return, you must send the Transmitter to an authorized Dexcom Technical Support Department. Make sure you package the Transmitter adequately for shipping.

The return package needs to include:

1. Transmitter
2. Sales receipt or comparable substitute proof of sale showing the date of purchase
3. Transmitter's Serial Number
4. Seller's name and address

Call Dexcom Technical Support Department for delivery information or help:

- Toll free: **1.877.339.2664**
- Charges may apply: **1.858.200.0200**

Upon receipt, Dexcom will promptly replace the defective Transmitter.

If Dexcom determines the Transmitter isn't covered by this Limited Warranty, Purchaser must pay all shipping charges for the Transmitter's return by Dexcom.

Limits on Dexcom's Warranty and Liability Obligations

The Limited Warranty described above is the exclusive warranty for the Transmitter, and in lieu of all other warranties, expressed or implied, either in fact or by operations of law, statutory or otherwise.

Dexcom expressly excludes and disclaims all other warranties, including without limitation any warranty merchantability, fitness for a particular purpose, or non-infringement, except to the extent prohibited by applicable law.

Dexcom shall not be liable for any special, incidental, consequential, or indirect damages, however caused, and on any theory of liability, arising in any way out of the sale, use, misuse, or inability to use, any Dexcom G5 Mobile CGM System or any feature or service provided by Dexcom for use with the Dexcom G5 Mobile CGM System.

These limits on Dexcom's warranty and liability obligations apply even if Dexcom, or its agent, has been advised of such damages and notwithstanding any failure of essential purpose of this Limited Warranty and the limited remedy provided by Dexcom.

This Limited Warranty is only provided to the original Purchaser and can't be transferred to anyone else, and states Purchaser's exclusive remedy.

If any portion of this Limited Warranty is illegal or unenforceable by reason of any law, such partial illegality or enforceability shall not affect the enforceability of the remainder of this Limited Warranty.

This Limited Warranty will be enforced to the maximum extent permitted by law.

Section 11

Travel

Dexcom G5 can be a great travel companion. Go through metal detectors, get hand-wanded, and even keep your receiver on during your flight.

This section only covers the Dexcom G5. It doesn't cover steps you need to take when traveling with your smart device. See your smart device's user guide for travel tips.

11.1 Going Through Security

Walk-Through Metal Detectors

Transmitter and Sensor

Go through walk-in metal detectors or be hand-wanded without worrying about damaging your transmitter or sensor.

If you're concerned or uncomfortable about walking through the metal detector, the Transportation Security Administration (TSA) requests you tell the Security Officer you're wearing a continuous glucose monitor and want a full-body pat-down with a visual inspection of your sensor and transmitter.

Let the Security Officer know the sensor can't be removed because it's inserted under the skin.

X-Ray Machines

Receiver, Extra Sensors

Don't put your Dexcom G5 components through baggage x-ray machines.

Before your screening process begins, ask the TSA Officer to perform a visual inspection of the receiver and your extra sensors. Place all Dexcom G5 components in a separate bag before handing over to the Security Officer.

For other medical supplies, such as medications, meters, and strips, check manufacturer's instructions or the TSA website.

Body Scanners

Use of AIT body scanners (also called millimeter wave scanners) has not been tested and may affect the system. Therefore, we recommend hand-wanding or full-body pat-down and visual inspection in that situation.

In the Plane

To use your smart device, receiver, or both to get sensor glucose information while in the plane:

- Smart device: When you switch to airplane mode, keep *Bluetooth* on
- Receiver: Keep receiver on

Contact your airline for their policies.

Technical Information

The Dexcom G5 System is an M-PED (Medical-Portable Electronic Device) which meets the FAA RTCA/DO-160 edition G section 21, Category M. It can be used on aircraft according to the directions provided by the operator of the aircraft.

Any M-PED that meets this standard in all modes may be used onboard the aircraft without any further testing by the operator.

This device can withstand exposure to common electrostatic discharge (ESD) and electromagnetic interference (EMI).

Still Have Questions?

Visit the TSA's website at tsa.gov if you have any questions or concerns at tsa.gov.

Email: TSA-ContactCenter@tsadhs.gov

Phone: 1.866.289.9673

Section 12

Need Help? You're Not Alone!

Dexcom has three support teams to help you, each with their own specialty:

- Technical Support Team
- Dexcom Care Team
- Sales Support Team

Want more information? Dexcom has numerous resources on its website.

12.1 Dexcom Technical Support

Provides replacement units, resolves technical issues or takes product complaints.

Call your Dexcom Technical Support Team, 24 hours a day, 7 days a week, if something is wrong with your Dexcom G5.

By Email

Email: TechSupport@dexcom.com

If you prefer to email, to help us help you best, include the following information in your email:

- Name of patient
- Date of Birth
- The technical issue you have
- When the problem happened (date and time)
- Patient's address
- Patient's phone number
- Item SKU number and description (e.g., name of the device)
- Lot number and/or serial number(s) of affected devices (e.g., sensor)

If you are using the Dexcom G5 Mobile App, use the app to email technical support:
Menu > **Help** > **Contact Dexcom** > **Technical Support** > **Email**

By Phone

Dexcom Technical Support Phone Numbers:

Toll Free: 1(b)(4)

Toll Call: (b)(4)

What Can They Help Me With?

The Dexcom Technical Support Team helps you with all CGM system related issues including CGM software issues.

Dexcom Technical Support does not offer medical advice.

12.2 Dexcom Care Team

The Dexcom Care Team is a group of Certified Diabetes Educators (CDE®) and Registered Nurses (RNs) offering you customer care and individualized education services around Dexcom CGM.

Dexcom Care provides education and support throughout your CGM experience, such as:

- Initial CGM Product Training
- Ongoing Dexcom product education (e.g., how to use a specific feature)
- How to maximize Dexcom CGM use
- Dexcom CGM reporting software and features
- How to review and understand Dexcom CGM reports

By Phone

Available Monday-Friday 6:00 am-8:00 pm PST (subject to change)

Toll Free: (b)(4)

Toll Call:

By Email

Email: patientcare@dexcom.com

If you prefer to email, to help us help you best, include the following information in your email:

- Name
- DOB
- Contact phone number
- Reason for inquiry or education needed

12.3 Sales Support Team

Inside Sales Support Team

For help with:

- First-time orders

(b)(4)

- Re-orders
- Tracking shipments
- Locating a local Dexcom representative

By Phone

Dexcom Inside Sales Support Phone Numbers:

Toll Free: (b)(4)

Toll Call:

By Email

Dexcom Inside Sales Support Email: CustomerService@dexcom.com

By Fax

1.877.633.9266

12.4 Corporate

Dexcom Website:
Dexcom.com

Dexcom Address:
6340 Sequence Drive
San Diego, CA 92121

12.5 Explore Web Based Education

Dexcom makes CGM education easier for you with interactive web-based education programs.

dexcom.com/web-based-education

12.6 Explore Share/Follow

See how you can share your CGM data with friends and family with Dexcom Share/Follow.

dexcom.com/apps

12.7 Frequently Asked Questions

Have questions? It may be answered in the FAQ section on the Dexcom website.

dexcom.com/**faq**

Index

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(b)(4) [redacted]

Be eligible to participate in a monthly drawing for a free box of sensors by completing this training business reply card within 14 days of training.

Dexcom®

Individuals are limited to a one-time prize redemption for a box of sensors. Health care professionals and Medicare patients who purchase the Dexcom G5 Mobile System are not eligible to participate. Winners will be notified by email.

seal

seal

Complete, sign, and return card to Dexcom via:

- Fax: (b)(4) [redacted]
- Email: **fieldclinicaltraining@dexcom.com**
- US mail

I have trained on the following:

- ☐ Dexcom G5 Mobile Components
- ☐ Display Device Options
- ☐ Setting High/Low Alerts
- ☐ Inserting Sensor
- ☐ Starting Sensor Session
- ☐ Entering BG Meter Value
- ☐ Ending Sensor Session

fold here

Fold over with the *Business Reply Mail* facing up and back is blank.

For your privacy, seal edges with tape.

Patient Name: _____

Patient Email: _____

Trained by:

☐ Self-Training/Tutorial ☐ Diabetes Center/Doctor's Office

☐ Dexcom Staff _____

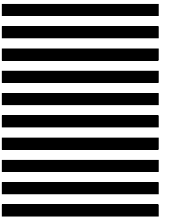
Date: _____

Physician Name: _____

Patient Signature: _____

seal for privacy

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES



BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO 28592 SAN DIEGO CA

POSTAGE WILL BE PAID BY ADDRESSEE

ATTN.: TRAINING DEPT.
DEXCOM, INC.
6340 SEQUENCE DR.
SAN DIEGO, CA 92121-9942

Dexcom G5® mobile

Your options to get the full Dexcom G5 Mobile User Guide:

1. Download as an eBook or view/print in a .pdf format
   dexcom.com/guides
2. Online request form to receive a free printed copy
   dexcom.com/guides
3. Request a free copy by mail
   Cut this page along the dotted lines on the left.
4. Request a free copy by phone
   (b)(4) [redacted]

seal

seal

Fold over with the *Business Reply Mail* facing up and back is blank.

For your privacy, seal edges with tape.

fold here

Mail-In Request for Dexcom G5 Mobile CGM User Guide

YES! Please send me a printed Dexcom G5 Mobile CGM User Guide

Patient Name: _____

Patient Address: _____

Address Line #2: _____

City: _____State:_____Zip _____-_____

Phone Number:_(_____)_____

seal for privacy

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO 28592 SAN DIEGO CA

POSTAGE WILL BE PAID BY ADDRESSEE

PLACEHOLDER

ATTN.: TRAINING DEPT.
DEXCOM, INC.
6340 SEQUENCE DR.
SAN DIEGO, CA 92121-9942

Dexcom®

Dexcom, Inc.
6340 Sequence Drive
San Diego, CA 92121 USA

(b)(4)

Web: dexcom.com

LBL013446 Rev 003 MT23436

The tutorial can be accessed by accessing this website:

(b)(4)

Please use the following username and password to view the tutorial:

(b)(4)

SECTION 4

Appendix – Literature References

ORIGINAL ARTICLE

Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group*

ABSTRACT

BACKGROUND

The value of continuous glucose monitoring in the management of type 1 diabetes mellitus has not been determined.

METHODS

In a multicenter clinical trial, we randomly assigned 322 adults and children who were already receiving intensive therapy for type 1 diabetes to a group with continuous glucose monitoring or to a control group performing home monitoring with a blood glucose meter. All the patients were stratified into three groups according to age and had a glycated hemoglobin level of 7.0 to 10.0%. The primary outcome was the change in the glycated hemoglobin level at 26 weeks.

RESULTS

The changes in glycated hemoglobin levels in the two study groups varied markedly according to age group (P=0.003), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change, −0.53%; 95% confidence interval [CI], −0.71 to −0.35; P<0.001). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08; 95% CI, −0.17 to 0.33; P=0.52) or among those who were 8 to 14 years of age (mean difference, −0.13; 95% CI, −0.38 to 0.11; P=0.29). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe hypoglycemia was low and did not differ between the two study groups; however, the trial was not powered to detect such a difference.

CONCLUSIONS

Continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes. Further work is needed to identify barriers to effectiveness of continuous monitoring in children and adolescents. (ClinicalTrials.gov number, NCT00406133.)

The members of the writing committee (William V. Tamborlane, M.D., Roy W. Beck, M.D., Ph.D., Bruce W. Bode, M.D., Bruce Buckingham, M.D., H. Peter Chase, M.D., Robert Clemons, M.D., Rosanna Fiallo-Scharer, M.D., Larry A. Fox, M.D., Lisa K. Gilliam, M.D., Ph.D., Irl B. Hirsch, M.D., Elbert S. Huang, M.D., M.P.H., Craig Kollman, Ph.D., Aaron J. Kowalski, Ph.D., Lori Laffel, M.D., M.P.H., Jean M. Lawrence, Sc.D., M.P.H., M.S.S.A., Joyce Lee, M.D., M.P.H., Nelly Mauras, M.D., Michael O'Grady, Ph.D., Katrina J. Ruedy, M.S.P.H., Michael Tansey, M.D., Eva Tsalikian, M.D., Stuart Weinzimer, M.D., Darrell M. Wilson, M.D., Howard Wolpert, M.D., Tim Wysocki, Ph.D., and Dongyuan Xing, M.P.H.) assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Beck at the Jaeb Center for Health Research, 15310 Amberly Dr., #350, Tampa, FL 33647, or at rbeck@jaeb.org.

*The affiliations of the members of the writing committee and those of investigators in the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group are listed in the Appendix.

This article (10.1056/NEJMoa0805017) was published at www.nejm.org on September 8, 2008.

N Engl J Med 2008;359:1464-76.

Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry

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To examine the overall state of metabolic control and current use of advanced diabetes technologies in the U.S., we report recent data collected on individuals with type 1 diabetes participating in the T1D Exchange clinic registry. Data from 16,061 participants updated between 1 September 2013 and 1 December 2014 were compared with registry enrollment data collected from 1 September 2010 to 1 August 2012. Mean hemoglobin A_{1c} (HbA_{1c}) was assessed by year of age from <4 to >75 years. The overall average HbA_{1c} was 8.2% (66 mmol/mol) at enrollment and 8.4% (68 mmol/mol) at the most recent update. During childhood, mean HbA_{1c} decreased from 8.3% (67 mmol/mol) in 2–4-year-olds to 8.1% (65 mmol/mol) at 7 years of age, followed by an increase to 9.2% (77 mmol/mol) in 19-year-olds. Subsequently, mean HbA_{1c} values decline gradually until ~30 years of age, plateauing at 7.5–7.8% (58–62 mmol/mol) beyond age 30 until a modest drop in HbA_{1c} below 7.5% (58 mmol/mol) in those 65 years of age. Severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) remain all too common complications of treatment, especially in older (SH) and younger patients (DKA). Insulin pump use increased slightly from enrollment (58–62%), and use of continuous glucose monitoring (CGM) did not change (7%). Although the T1D Exchange registry findings are not population based and could be biased, it is clear that there remains considerable room for improving outcomes of treatment of type 1 diabetes across all age-groups. Barriers to more effective use of current treatments need to be addressed and new therapies are needed to achieve optimal metabolic control in people with type 1 diabetes.

Results of the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the DCCT cohort have demonstrated that most people with type 1 diabetes should be treated intensively to achieve hemoglobin A_{1c} (HbA_{1c}) levels as close to normal as possible and as early in the course of the disease as possible to prevent and delay the late micro- and macrovascular complications of the disease (1). Most recently, the DCCT/EDIC study group reported that all-cause mortality also was reduced over 30 years of follow-up during DCCT/EDIC in the original DCCT intensive treatment group compared with the original conventional treatment group (2). Consequently, the American Diabetes Association (ADA) treatment guidelines indicate that adults with type 1 diabetes should aim at target HbA_{1c} levels <7.0% (53 mmol/mol) unless there is a reason, such as recurrent severe hypoglycemia (SH), to set a higher target, whereas the target is set slightly higher in children and adolescents at <7.5% (58 mmol/mol) by both the ADA and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (3,4).

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