Initiation of Continuous Glucose Monitoring at Diagnosis of Type 1 Diabetes
Version 1.3 (Version that Received FDA Approval)
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CHAPTER 1: INTRODUCTION

1.1. Purpose

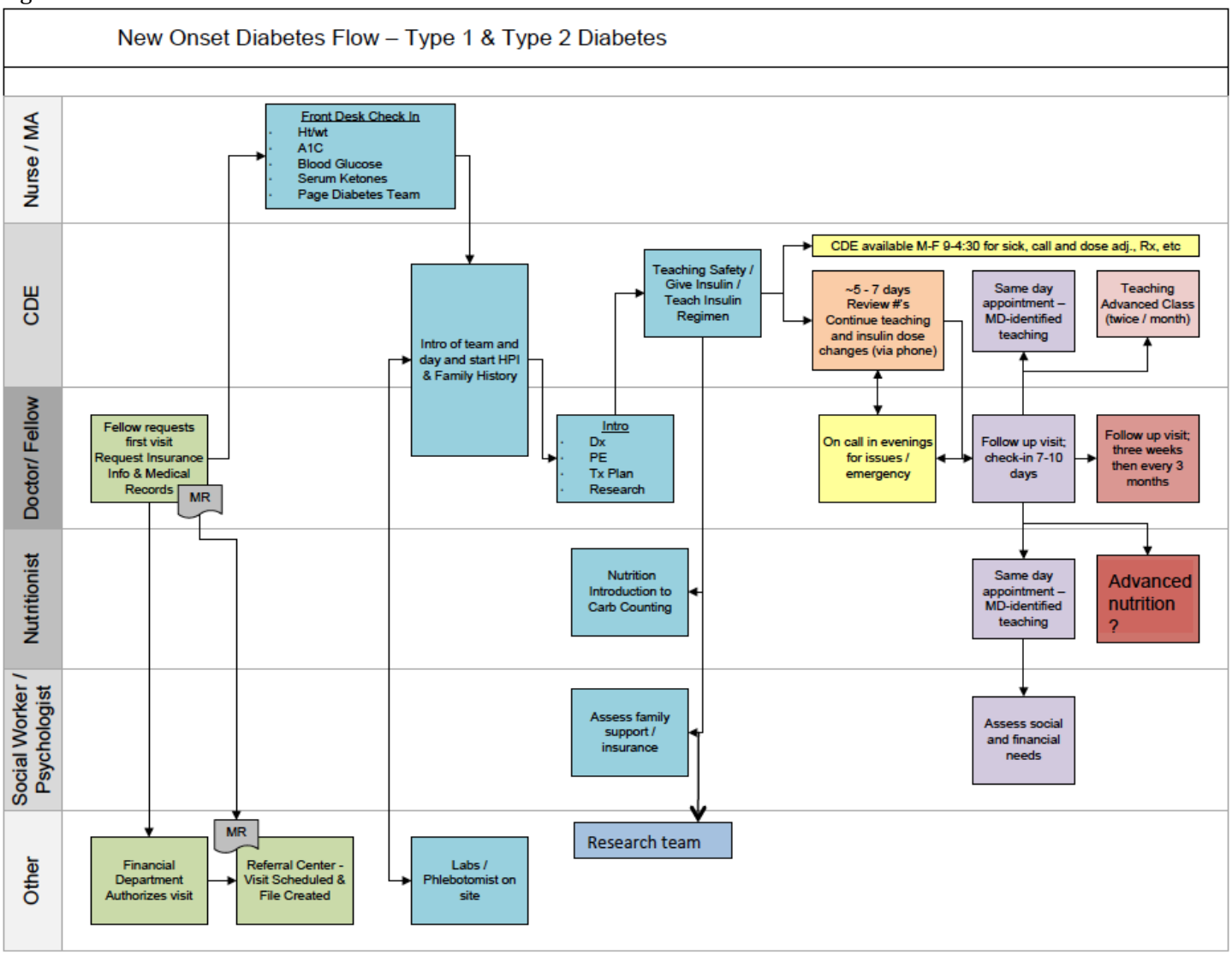
The primary objective of this pilot project is to examine the impact of continuous glucose monitoring (CGM) on families with newly diagnosed children with type 1 diabetes (T1D). This randomized clinical trial compares newly diagnosed T1D youth who are started on CGM (the intervention group) versus those who are not (the control group). We will examine group differences over a 6-month period (Phase 1) on two sets of outcomes. The first set of outcomes includes psychosocial variables such as parents' diabetes-related distress, hypoglycemic concerns, broad markers of parent stress, anxiety and sleep quality, and health-related quality of life. In this set of psychosocial outcomes, health-related quality of life is the identified primary endpoint. The second set of outcomes includes glycemic variables such as time spent in range, hemoglobin A1c, and C-peptide. In this set of glycemic outcomes, time spent in target range is the identified primary endpoint. After the initial comparison of intervention to control across the first six months after diagnosis, we will conduct a longitudinal follow-up (Phase 2) of glycemic and psychosocial variables for an additional 18 months.

1.2. Background

1.2.1. Current landscape of type 1 diabetes management. Type 1 diabetes management is complex and demanding. The T1D regimen requires frequent blood glucose monitoring, precise timing and dosing of insulin administration, and consideration of dietary intake and physical activity. Each individual task by itself is demanding, but the integration of them all adds a high degree of complexity. Achieving optimal diabetes control remains elusive for many families with children with T1D [1,2].

1.2.2. Current approaches to diabetes treatment in newly diagnosed youth. There is some variability with treatment approaches in the United States. However, most diabetes centers base their standards of care on the Clinical Practice Guidelines published annually by the American Diabetes Association in *Diabetes Care*. That is the case for both clinical sites in this study. A general framework of diabetes care initiated at diagnosis of type 1 diabetes is depicted in Figure 1 using a swim lane diagram. While this is specific to care delivered at Stanford, this is the same approach to care delivered at the Barbara Davis Center.

Figure 1. New Onset Flow Chart



The diabetes clinics at Stanford and Barbara Davis Center both initiate treatment with multiple daily injections of rapid acting insulin analogs and 1-2 injections per day of long acting insulin (glargine or detemir). At both sites, basal-bolus regimens are the first line of insulin treatment and frequent monitoring (over the phone or email) and face-to-face visits with the clinical care team will help to fine-tune dosages. Parents and youth (typically starting at age 10) are taught procedures for injecting insulin as well as time periods to check blood sugar to understand insulin action. They are discouraged from administering rapid acting insulin unless three hours have passed (i.e., avoid insulin stacking). In addition to nutrition therapy via carbohydrate counting, families are recommended to do 6-10 fingersticks per day to monitor blood sugars. Substantial education is provided through additional materials including *Understanding Diabetes* (known to many as the Pink Panther book) written by Drs. Peter Chase and David Maahs at the Barbara Davis Center. The 13th edition of this book is given to new onset families and also accessible online at the Barbara Davis Center website (www.barbaradaviscenter.org) under online books. Both sites give this book to new onset families. In addition, supplemental education handouts are typically provided as well by the diabetes education. As an example, the supplemental education materials from the Stanford site are included in the Appendix.

With CGM and insulin pump use becoming more common, more families are interested in adding these technologies to the treatment regimen sooner. Many providers do not start using CGM or insulin pumps until at least 3-6 months after diagnosis and previous wisdom was to wait until at least 12 months from diagnosis to move to the insulin pump. Even if a family with experience in treating type 1 diabetes (such as a parent or sibling with

T1D), insurance may reject coverage for insulin pumps and CGM prior to 6 months of T1D diagnosis. Research data on the initiation of CGM use soon after diagnosis would be helpful to update and possibly improve on the treatment of newly diagnosed youth with T1D.

1.2.3. Evidence of safety and efficacy of CGM. Recent data suggest that youth with T1D using CGM can achieve lower hemoglobin A1c values and experience fewer hypoglycemic events than non-CGM-using youth [3,4]. Even with relatively older and less reliable CGM systems, parents of youth with T1D often reported relatively high levels of satisfaction. However, little else is known about parents' responses to CGM. We do know that parents of youth with T1D are often highly distressed at diagnosis and over the course of many years, partly due to their sense of powerlessness in the face of often wild swings in their child's mood and glucose levels as well as their fears and worries concerning the ever present danger of hypoglycemia [5-7]. A goal of this project is to better understand whether the introduction of CGM in youth with T1D at diagnosis might allay parents' fears, more broadly ease their sense of diabetes-related distress and foreboding, and impact glycemic variables measured during the first year of T1D.

1.3. Preliminary studies

We have extensive experience using sensors, pumps, and new technology. Both the Stanford and University of Colorado groups participated in the NIH sponsored metabolic control at the onset of diabetes study where newly-diagnosed children received three days of closed-loop therapy within a week of diagnosis and then were maintained on sensor augmented pump therapy for one year [8]. Stanford and University of Colorado were two of the three centers conducting the predictive low glucose suspend (PLGS) in-home studies [9] and have worked together on DirecNet studies and the JDRF randomized clinical trial of CGM, as well as full day and night closed-loop studies using automated delivery systems.

All of the investigators involved in these studies have extensive experience in continuous glucose monitoring and artificial pancreas development. Our study groups have worked well together since the onset of the NIH-funded Diabetes Research in Children Network (DirecNet). Since 2001 DirecNet has conducted numerous protocols involving CGM in which both centers participated in equally. Both centers also were leaders in the JDRF-funded CGM Randomized Clinical Trial (RCT) comparing CGM to standard care [10]. Dr. Buckingham was the PI at Stanford on the STAR-1 randomized trial of continuous glucose monitoring [11]. Drs. Chase and Slover at the University of Colorado were major participants in the STAR-3 trial of sensor augmented pumps. Dr. David Maahs was the PI for the recent treat-to-range studies at the University of Colorado. As part of these studies, we all have gained extensive experience using the Medtronic Paradigm REAL-Time Insulin Pump and CGM System.

The Metabolic Control study (IDE G080204) was an NIH-sponsored study to determine if tight glucose control beginning within the first week of diagnosis of diabetes will be of benefit in maintaining endogenous insulin production. We have over 700 hours of experience using this system at Stanford, and two of the centers doing this study (Stanford and University of Colorado) have amassed over 1,400 hours of inpatient data without any severe adverse events.

In a recent pilot study conducted at Stanford, Barbara Davis Center, and Indiana University (PIs Buckingham & Hood) called *Using Behavioral Supports for Diabetes Devices in Young Children with Type 1 Diabetes*, 17 families with a child under the age of 6 with type 1 diabetes were enrolled. All participants were on CGM and as part of assessment procedures, parents completed food, insulin, and meter blood glucose logs (7 days pre-intervention and 7 days post-intervention). On those logs, 8 noted they were using non-adjunctive CGM data to make diabetes treatment decisions. Logging of this information was not required as part of the study and it is not known if the 9 participants who did not indicate so had used non-adjunctive CGM data to make treatment decisions. The age range of the 8 participants who had indicated non-adjunctive CGM use at the time of enrollment was 2 to 5 years. Duration of diabetes was between 1.08 and 4.67 years (mean 2.25, SD 1.13 years). Frequency of CGM use prior to study enrollment ranged from 7 to 30 days per month (mean 26 days, SD 8.39 days). Over 90% were using the Dexcom G4 system, some with active Share remote monitoring.

In sum, our research teams have a great deal of experience utilizing diabetes devices and technologies, including CGM, in young people with T1Dand we have collaborated extensively in the past.

CHAPTER 2: STUDY PROTOCOL

2.1. Synopsis of study protocol

This pilot randomized clinical trial compares newly diagnosed T1D youth who are started on CGM (the intervention group) versus those who are not (the control group). We will examine group differences over a 6-month period (Phase 1) on two sets of outcomes: psychosocial variables and glycemic variables. After the initial comparison of intervention to control across the first six months after diagnosis, we will conduct a longitudinal follow-up (Phase 2) of glycemic and psychosocial variables for an additional 18 months. The CGM system used in this study is the Dexcom G5 System with the Share function (FDA Approved). An IDE will be obtained to use this system in a non-adjunctive manner. Participants will complete Phase 1 in six months. Phase 2 includes 3 more assessments conducted every six months until participants are two years post-diagnosis.

2.2. Study Procedures

Participants will be recruited at two centers: Stanford University and the Barbara Davis Center for Diabetes, University of Colorado. Participants will be enrolled while inpatient or within 1 month of diagnosis. Based on data over the past year, we anticipate at least 15 new diagnoses each month at these two centers, with at least 10 in the eligible age range. Once identified, study staff will approach potential participants to explain the study, determine eligibility, and obtain informed consent. Once enrolled in the study, participants will be randomized. We will randomize at a 2:1 ratio, intervention to control. We will also stratify by age group to ensure equal representation of ages across groups. The age groups (in years) are 2-6, 7-11, and 12-17. To ensure safety in the youngest group, recruitment of participants in the age 2-6 years group will not begin until we have at least 2 weeks of non-adjunctive CGM use data in at least 3 participants aged 7-17 years. Data will be reviewed by the DSMB on these 3 participants and if deemed safe by the DSMB, we will start enrolling participants in the youngest age group.

2.3. Study Groups

There are two groups in this pilot study: intervention and control. After randomization, participants in the intervention group (CGM) will receive standardized education about CGM and its use. This session can take up to 120 minutes and will focus largely on adjunctive use and other foundational aspects of education about CGM use. After a two-week period of adjunctive use, families will receive another training (up to 120 minutes) that will reinforce some of the content on CGM use and introduce and train on non-adjunctive use of the Dexcom G5 system. The procedures for non-adjunctive use are detailed below in section 2.5. and families will be informed that they have the freedom to check and rely on blood glucose via fingerstick any time the child or parent notices a potential discrepancy between CGM and fingerstick values. Families will be given handouts that contain information in sections 2.5. Families will also be provided with accuracy tables 3-D, 11-B, and 12-B from the Dexcom manual and will be instructed on the accuracy of sensor values at different readings. This information, along with all that is given as handouts to study participants, will also be given to the healthcare team. A person trained in delivering education about CGM will deliver the education about CGM use and will insert the first sensor at the first training. This individual will be available to assist with questions from participating families. In addition, Dexcom representatives are available to the family for technical questions or issues with the system, just like the access any Dexcom user has. Families randomized to the intervention group will be required to actively use CGM for 6 months. After six months, they can continue or discontinue use of CGM. If they decide to continue, the study team will work with the diabetes care team to assist them with obtaining CGM via the standard clinic and insurance procedures.

Families randomized to the control group will receive usual care for T1D and take part in blinded CGM one week per month. Blinded CGM use entails insertion of a Dexcom sensor and calibration of the system using blood glucose meter values at system start up, every 12 hours thereafter, and any time the system requests a calibration value. At six months, they will receive training and supplies for the next six months to start non-adjunctive use of CGM. They will receive the exact training, education, and monitoring delivered to the intervention group and described earlier in this section. At 12 months, if they decide to continue to use CGM, the study team will work with the diabetes care team to assist them with obtaining supplies via the standard clinic and insurance procedures.

2.4. Rationale for non-adjunctive use of CGM in this study

The use of CGM in newly diagnosed youth with T1D offers a unique opportunity to teach diabetes management in the manner that is expected to be more common in several years. Increasingly, individuals with T1D who use CGM make treatment decisions based on the information obtained from CGM instead of fingerstick glucose values done by blood glucose meters. Further, as the safety and accuracy of these CGM systems has improved and can actually surpass the accuracy of many meters, more treatment decisions are made in a non-adjunctive manner.

The Dexcom G5 System with Share is FDA approved and this Dexcom system and all other CGM systems approved by the FDA are indicated for use as adjunctive devices. The Dexcom G5 Mobile system is approved via a CE mark for non-adjunctive use and can be used as the primary source of glucose information for diabetes management. In other words, information about glucose levels provided by CGM can be used to make diabetes treatment decisions. Thus, there are trends toward non-adjunctive use of CGM in both patient populations and from industry. This study will provide data on non-adjunctive use and provides a unique group to test this in – individuals who do not have working knowledge of adjunctive use or blood glucose meter treatment decisions.

2.5. Procedures for non-adjunctive Use of CGM

Participants in this study will be taught to use CGM in a non-adjunctive manner that is consistent with the language included in Dexcom's CE mark. Participants – youth with T1D and their caregivers – will be taught the following in their initial education session with CDE and will be provided with this information in a handout. Of note, participating families are able to seek out other devices (e.g., insulin pump) and start them during the course of the study. We will track this information, but neither encourage or discourage use. The study-specific CGM education and informational handout will be provided by the research team. The study team (CDE in particular) will review the following guidelines and note that alert and alarm settings on the CGM system should be set in consultation with the diabetes care team.

<u>Instructions for non-adjunctive CGM use with Dexcom G5 Share</u>

1. 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.

2. Discuss with a healthcare provider on your study team how you should use the information displayed on the Dexcom G5 to help manage your diabetes.

3. Taking medications with acetaminophen while wearing the Dexcom G5 may lead to inaccurate 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 CGM data produced by the Dexcom G5 if you have recently taken acetaminophen. Keep in mind that some cold medicines contain acetaminophen. If you are not sure if your medication contains acetaminophen, contact your health care provider before taking the medication.

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

5. 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.

6. 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.

7. Make diabetes treatment decisions based on the combination of the sensor glucose reading, trend arrow, trend graph, and/or actionable alerts generated by the Dexcom G5. If you plan to administer insulin for a sensor glucose reading over 300 mg/dl, you should be conservative with dosing and possibly double-check sensor value with fingerstick blood glucose before administering a correction dose.

8. If your sensor glucose is below 40 mg/dl, you get a "LOW" on your display device. You may have very low blood sugar requiring immediate treatment based on your health care professional's guidance. To be safe, treat first. After treating, make sure your glucose is very low by doing a fingerstick for a BG measurement.

9. If your sensor glucose is above 400 mg/dl, you get a "HIGH" on your display device. You may have very high blood sugar requiring immediate treatment based on your health care professional's guidance. To be safe, first make sure your glucose is very high and do a fingerstick for a BG measurement. Treat based on your BG measurement.

There are three keys when making decisions based on your Dexcom G5. Without all three, you won't have all the needed information to make a correct treatment decision.

To help you remember the three key pieces, think of TAG:

T-Trend: Trend Dots

Make sure trend graph has three back-to-back readings within the last 15 minutes

A-Arrow: Trend Arrow

Your trend arrow telling you the speed and direction of your glucose

G-Glucose: Sensor Glucose Readings

If you do not have TAG do not make any treatment decisions using your Dexcom G5

Possible Scenarios to use TAG:

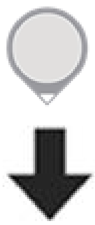
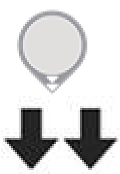
Scenario 1: You have consistent trend dots for the past hour (T), the arrow is to the right ➡ (A), and the glucose reading is 243 mg/dl. In this situation, you first consider whether you need to administer a correction insulin dose because you have consistent information and a flat arrow to the right showing steady sensor values. In this situation, you would check to see if any rapid acting insulin has been administered in the past 3 hours. If so, you will wait until the three hours is up and then re-assess using TAG. If it has been 3 hours or longer since the last rapid acting insulin injection (or bolus), you will plug the sensor value in to the equation you came up with your clinical care team and decide on the appropriate insulin dose.

Scenario 2: You do not have all three pieces of information for TAG and want to administer insulin. In this case, you will resort back to blood glucose readings and make treatment decision based on rules provided by your clinical care team.

Scenario 3: You have consistent trend dots for at least the past 15 minutes (T) and your glucose reading is 174 mg/dl (G). Your trend arrow is straight down  (A). Before administering insulin or taking fast-acting carbohydrates, you should "watch and wait" for 15 minutes and re-assess TAG at that time. Do not administer insulin until you no longer have a down arrow. Possibly treat with fast-acting carbohydrates if sensor value approaches your low threshold or the arrow is still going straight down.

Table 1. Possible actions based on sensor glucose reading and trend arrows

Screen	Possible actions based on sensor glucose reading's trend arrows		
Arrows	Low Glucose	High Glucose	Target Glucose
	No arrows/no sensor glucose readings. Use BG meter, not Dexcom G5, to make treatment decision.	No arrows/no sensor glucose readings. Use BG meter, not Dexcom G5, to make treatment decision.	No arrows/no sensor glucose readings. Use BG meter, not Dexcom G5, to make treatment decision.
	May need to eat a snack or a fast acting carbohydrate.	May adjust insulin to correct a high sensor glucose reading to reach target range. Do not take multiple insulin doses too close together in time. Think about your trend graph and recent Alarm/Alerts.	Based on last meal or insulin dose, may need to take insulin or eat a snack to stay within target. Do not take multiple insulin doses too close together in time.
	Watch and wait.	May adjust insulin to correct a high sensor glucose reading to reach target range. Do not take multiple insulin doses too close together in time. Think about your trend graph and recent Alarm/Alerts.	Based on last meal or insulin dose, may need to take insulin to stay within target. Do not take multiple insulin doses too close together in time.
	Watch and wait. Make sure you did not over treat for a low.	May adjust insulin to correct a high sensor glucose reading to reach target range. Do not take multiple insulin doses too close together in time. Think about your trend graph and recent Alarm/Alerts.	If not with a recent meal or snack, may take insulin to stay within target range.
	Watch and wait. Make sure you did not over treat for a low.	May adjust insulin to correct a high sensor glucose reading to reach target range. Do not take multiple insulin doses too close	May need to take insulin to stay within target. Do not take multiple insulin doses too close together in time.

		together in time. Think about your trend graph and recent Alarm/Alerts.	
	May need to eat a snack or fast acting carbohydrate. Was last insulin dose too high or activity too strenuous?	Based on last insulin dose or activity, may need to watch and wait to reach your target range. Think about your trend graph and recent Alarm/Alerts.	May need to eat a snack or fast acting carbohydrate.
	May need to eat a snack or fast acting carbohydrate. Was last insulin dose too high or activity too strenuous?	Based on last insulin dose or activity, may need to watch and wait to reach your target range. Think about your trend graph and recent Alarm/Alerts.	May need to eat a snack or fast acting carbohydrate.
	May need to eat a snack or fast acting carbohydrate. Was last insulin dose too high or activity too strenuous?	Based on last insulin dose or activity, may need to watch and wait to reach your target range. Think about your trend graph and recent Alarm/Alerts.	May need to eat a snack or fast acting carbohydrate.

2.6. Coordination of Study Procedures with Clinical Care

All study participants will receive clinical care by staff in their respective diabetes centers. Staff at both sites include pediatric endocrinologists, nurses, nurse practitioners, certified diabetes educators, social workers, psychologists, and dietitians. As noted and depicted earlier in section 1.2.2., care for newly diagnosed youth with type 1 diabetes and their families includes frequent contact, extensive education, and materials and guides provided to all families. Clinical care teams will teach families who enroll in this study about insulin administration, nutrition therapy (e.g., carbohydrate counting), and blood glucose monitoring. If families start on an insulin pump during the course of the study, that will be coordinated by the clinical care team and study staff will not be part of that decision making or training. In sum, care for new onset type 1 diabetes will be delivered by the clinical care team and this care is consistent with clinical practice guidelines and clinician expertise.

The study staff has the primary role of initiating CGM (at the start of the study with intervention participants and after six months with control participants) and training participants on non-adjunctive use. Clinical care staff will be informed about which of their clinic patients are study participants and which are actively engaged in non-adjunctive use of CGM. The clinical care team will also be provided with the educational materials given to study participants. The clinical care team will be informed about use of Dexcom software so that they may review study

participant CGM data. Further, the following scenarios may be encountered and if they occur, they will be reported to the clinical care team:

- Upon review of CGM, more than 5% of values fall below the threshold for hypoglycemia (≤60 mg/dl).
- Upon review of blood glucose meter downloads (all participants), more than 10% of values fall below the threshold for hypoglycemia (≤60 mg/dl).
- Any evidence of insulin stacking reported by participants to study staff or apparent on a download (if download includes any insulin administration details).

2.7. Study Visits and Measurements

Study visits for both groups will occur at baseline, 13 weeks, and 26 weeks post randomization in Phase 1. Baseline is the date they complete the first assessment, which will have to be within the first month since diagnosis of T1D. These visits should be within ±2 weeks of the scheduled visit and will typically be done before or after a scheduled diabetes center outpatient visit. All participants receive these 3 comprehensive assessments.

After the initial six-months of the study, we will obtain data from participants at 12, 18, and 24 months post-diagnosis (Phase 2). We will conduct these assessments to examine changes over time in glycemic and psychosocial variables.

Assessment components are included in Table 2 for Parents and Table 3 for Youth.

Table 2. Assessment battery for Parents

Measure	Construct Measured / Relevant Points	Number of Items / Time to Complete
Psychosocial Outcomes		
Parents' Diabetes Distress	The Problem Areas in Diabetes, Pediatric version (PAID-P). The PAID-P is a validated tool used to assess parental burden related to diabetes management. The Parent Diabetes Distress Scale (PDDS). This is a validated tool to assess how diabetes care impacts on parents' quality of life.	20 items. 5-10 minutes to complete. 6 items, 2 – 3 minutes to complete.
Parents' Psychological Distress	The PHQ-9 and the State-Trait Anxiety Inventory will be used to assess depressive and anxiety symptoms. These symptoms represent the general construct of psychological distress.	9 items on PHQ-9 (5 minutes) and 40 items on STAI (10 minutes)
Parents' Sleep Quality	An abbreviated version of the Pittsburgh Sleep quality Index, a validated tool for assessing self-reported sleep quantity and quality, will be developed for this project.	7 items, 2 – 3 minutes to complete.
Parents' Hypoglycemic Fear	The Hypoglycemic Fear Survey-Parents (HFS-P) is a validated tool to assess parents' anxiety and behavior concerning possible hypoglycemia.	25 items, 5 – 10 minutes to complete
Parents' Hypoglycemic Confidence	A new version of the Hypoglycemic Confidence Questionnaire, modified for use by parents, will be developed for this project.	7 items, 2 – 3 minutes to complete
Health-related quality of life	Parents will complete the generic version of the Pediatric Quality of Life Inventory (PedsQL) to provide a report of their perception of the child's quality of life. This cuts across social, emotional, academic, and health domains.	25 items. 5-10 minutes to complete.
Satisfaction with Diabetes Technology	We will use our CGM Satisfaction Scale from JDRF and DirecNet studies (developed by Tim Wysocki, PhD). The Glucose Monitoring System Satisfaction Survey (GMSS-T1D) is a validated tool used to assess treatment satisfaction with glucose monitoring devices and its impact on quality of life and other patient-reported outcomes.	43 items. 5-10 minutes to complete. 15 items. 5-10 minutes to complete.

Use and Comfort with Technology	Objective questions documenting the frequency of use and types of technologies used. Both general (e.g., smartphone) and diabetes-specific (e.g., trend program).	20 items. 5 minutes to complete.
Demographic and Family Data	Parents will complete a questionnaire on the family's structure, racial and ethnic background, indicators of socioeconomic status, insurance status (public vs. private), and other essential characteristics.	5 minutes
Behavioral Outcomes		
Diabetes management behaviors	Blood glucose monitoring frequency (by meter download); adherence to injections/pump boluses;	Download (no time burden for participants)
Health care utilization	Number of visits and calls to the diabetes care team	Tracking by interview (10 minutes to complete)
Placement of sensor	Parents will log placement of sensor based on Dexcom manual table on page 75. A quadrants on the front abdomen and B locations on back of body will be noted.	

Table 3. Assessment Battery for Youth

Measure	Construct Measured / Relevant Points	Number of Items / Time to Complete
Psychosocial Outcomes		
Diabetes Distress	The Problem Areas in Diabetes (PAID) – Teen, Diabetes Burden is a measure of diabetes-specific burden. Items focus on degree to which diabetes impacts areas of everyday functioning. Strong correlations with clinical outcomes. The Diabetes Distress Scale (DDS) is a gold standard measure for understanding distress symptoms related to diabetes.	26 items. 7 minutes to complete. 17 items. 5 minutes to complete.
Psychological Distress	The Center for Epidemiologic Studies – Depression (CES-D) is a widely used measure to assess psychological distress	20 items. 5 minutes to complete.

	and depression.	
Health-Related Quality of Life	The Child Health Utility-9D (CHU-9D) is a pediatric generic preference based measure of health-related quality of life. The Pediatric Quality of Life Inventory (PedsQL) Diabetes module measures diabetes-specific health-realted quality of life.	9 items. 5 minutes to complete. 28 items. 5 minutes to complete.
Hypoglycemic Confidence	This 8 item survey has questions about the level of confidence that hypoglycemia can be addressed in different situations.	8 items. 3-4 minutes.
Health Literacy	The Diabetes Numeracy Test is a widely used measure of diabetes numeracy. This diabetes-specific measure has been shown to be linked with health outcomes and health literacy.	15 items. 5 minutes to complete.
Cognition (Attention, Executive Functioning, Processing Speed)	The NIH Toolbox offers standardized, validated assessments. Three modules are self-administered: The Flanker Inhibitory Control and Attention Test measures both a participant's attention and inhibitory control. The Dimensional Change Card Sort Test is a measure of cognitive flexibility. The Pattern Comparison Processing Speed Test measures speed of processing.	 3 minutes to complete. 4 minutes to complete. 3 minutes to complete.
Satisfaction with Diabetes Technology	We will use our CGM Satisfaction Scale from JDRF and DirecNet studies (developed by Tim Wysocki, PhD). The Glucose Monitoring System Satisfaction Survey (GMSS-T1D) is a validated tool used to assess treatment satisfaction with glucose monitoring devices and its impact on quality of life and other patient-reported outcomes.	43 items. 5-10 minutes to complete. 15 items. 5-10 minutes to complete.

Use of and Comfort with Technology	Objective questions documenting the frequency of use and types of technologies used. Both general (e.g., smartphone) and diabetes-specific (e.g., trend program).	20 items. 5 minutes to complete.
Behavioral Outcomes		
Diabetes Management Behaviors	The Diabetes Self Management Profile (DSMP) – Self Report is a validated tool used to assess daily diabetes management tasks including frequency of blood glucose monitoring, carbohydrate counting, and insulin administration.	24 items. 7 minutes to complete.
Health Outcomes		
HbA1c measurement	Participants will provide a small fingerstick sample of blood (capillary) during their routine clinic visit. This will be done using the DCA in clinic or local CTRU.	Gold standard measure of glycemic control
Glycemic excursion measures	Time in range (70 to 150 mg/dL); percent below 70 and 60 mg/dL as indicators of hypoglycemia, and above 150 and 250 mg/dL as indicators of hyperglycemia; additional indices of variability including standard deviation will also be calculated	
C-peptide	Fasting C-peptide collected at 0, 13, 52, and 104 weeks	4 blood draws over 24 months

In addition, parents will be asked to complete a brief online survey (< 10 minutes) at the following intervals since randomization – 4, 8, 18, and 22 weeks. These online surveys will consist of the Diabetes Distress Scale (3 items), PHQ-9 (9 items), and the short form of the STAI (10 items). Additional questionnaires will be administered at study conclusion to ascertain CGM satisfaction (both perceived benefits and barriers), overall usability issues, and amount of time the device was used. All surveys can be completed online via RedCap. Families will receive a $40 gift card for each assessment they complete. Participants 11-17 years of age will be asked to complete child/teen versions of several surveys. These include psychological distress, fear of hypoglycemia, and quality of life. They will not complete the phone call assessments. We will provide a $25 gift card to teens at each assessment.

The following table highlights the planned timeline for study visits.

Visit Number:	1	2	3	4	5	6	7	8	9	10
Study Time:	0	4w	8w	13w	18w	22w	26w	52w	78w	104w
History (medical and demographic)	X									
Training on use of CGM (intervention only)	X									
Adverse Events such as severe hypoglycemia		X	X	X	X	X	X	X	X	X

CGM downloads				X			X	X	X	X
Meter and CSII downloads (if applicable)				X			X	X	X	X
Training on use of CGM (control only)							X			
Local HbA1c	X			X			X	X	X	X
Fasting C-peptide	X			X				X		X
Full Psychosocial Questionnaires	X			X			X	X	X	X
Brief Online Psychosocial Survey		X	X		X	X				

In addition, participating families will be contacted once weekly for the first four weeks, and once every four weeks after to remind to upload Dexcom receiver via Dexcom Clarity website and software. The study team will provide technical assistance if required to upload the Dexcom receiver data.

2.8 Study population

The patient population is children with type 1 diabetes and their parents. Parents (18 years and older) will provide informed consent for their own participation and parental permission for their child to participate. Youth 11 years of age and older will provide assent for their own participation. In order to have at least 60 subjects complete the protocol, we will enroll up to 75 youth with newly diagnosed T1D and randomize them to either the intervention (CGM, n=50) or control group (no CGM, n=25).

2.8.1. Eligibility criteria

To be eligible for the study, a child must meet the following criteria:

1. Diagnosis of type 1 diabetes according to ADA diagnostic criteria
2. Time since diagnosis of no longer than one month
3. Age between 2 and 17 years
4. Parental consent (and assent from the child where applicable) to participate in the study
5. No severe medical conditions, which in the opinion of the investigators are likely to hinder participation in this clinical trial.

To be eligible for the study, a parent must meet the following criteria:

1. Parent or legal guardian of a child with type 1 diabetes meeting the "child" criteria outlined above
2. Age of 18.0 years or older
3. Parent comprehends written English
4. Parent understands the study protocol and signs the informed consent document

2.8.2. Exclusion criteria

The presence of any of the following is an exclusion for the study:

1. Child has a medical disorder that in the judgment of the investigator will interfere with completion of any aspect of the protocol (e.g., pregnancy, kidney disease, adrenal insufficiency, skin condition that may hinder sensor application).

2. Child has a neurologic disorder that in the judgment of the investigator will affect completion of the protocol

3. Current use of oral glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study
4. Child is unable to completely avoid acetaminophen for duration of study

2.9. Data Analysis Plan

Our team has extensive experience in database design and implementation, use of web-based assessment, data management, and data analysis. We will utilize the RedCap survey system to format all measures in to electronic form for completion online or in-person via computer or iPads. Data collected from participants will be housed on the RedCap server, which is encrypted and HIPAA-compliant, with secure access for unique study IDs assigned to each participant. RedCap survey data is then ready for download by study staff and will be imported to SAS 9.3 for data cleaning and analysis.

First, we will document uptake of the study with a review of descriptive statistics for all relevant metrics (e.g., recruitment rate, proportion enrolled relative to patient population) as well as indicators of the acceptance of randomization and overall intervention components (i.e., is there variability in retention and satisfaction between treatment arms?). When needed, data will be displayed graphically using spaghetti plots for individual as well as grouped data.

Second, in order to determine the preliminary efficacy of the intervention condition (CGM) compared to the control condition (standard care), linear mixed effects models will be used. A model will be run for each of the main endpoints, psychosocial distress and glycemic indices. The testable covariate in both cases will be treatment status (intervention or control). Linear mixed effects models were deemed most appropriate for these analyses due to the continuous nature of the variables, the longitudinal nature of the design, and our interest in testing within-individual change over time. PROC MIXED in SAS will be used for the linear modeling.

In general, if missing data are realized, these linear models allow for data that are missing at random to be handled appropriately by incorporating relevant variables in the statistical model. We will also assess the degree of non-ignorable missingness present through investigating and reporting the impact of sensitivity analyses (e.g., pattern mixture models[8]) that allow for plausible non-ignorable missing data patterns on the model results.

A total of 60 participants with newly diagnosed T1D will be enrolled. This sample size is based on our projections of ease in recruiting in the two clinical centers across the study time frame, the pilot nature of the proposed research, and sufficient sample size to project effect sizes for the larger efficacy trial. We are mindful of caution raised by biostatisticians in underestimating sample size for pilot clinical trials[9] and thus have been conservative in our estimates. The estimate of 60 participants is predicated upon a longitudinal two-group test of significance with 4 time points, an effect size of 1σ on psychological distress and glycemic indices, up to 10% attrition at follow-up, and 80% power. Recognizing that estimates from small samples are imprecise, we will cautiously use summary measures from the pilot study to help determine the appropriate sample size for a larger trial, including effect sizes and the standard deviations of continuous outcome measures.

2.10. Expected duration of study participation

Duration of study participation is expected to be 2 years.

CHAPTER 3: ADVERSE EVENT REPORTING AND SAFETY MONITORING

3.1. Overview of Safety Monitoring

Study procedures are in place to monitor safety of participants and reduce risk for adverse events. These procedures come in two forms: those conducted by the study staff and conveyed to study participants, and those conducted by the study staff and conveyed to their diabetes care team. All participants will have glucose data reviewed at planned intervals and based on pre-determined cut points to determine safety.

All participants, intervention and control, will have their glucose data reviewed weekly by study staff for the first month of study participation. All participants in the intervention group will have their CGM data reviewed daily in their first week of non-adjunctive CGM use (week 3 of the study). Those on CGM will be monitored via Dexcom Clarity download and those using only meters (control group) will be done via meter download (or review of faxed or emailed logbooks if family is not able to download meter at home). After the first month, this occurs once monthly, starting on week 6 of the study,for the remaining 5 months. The control group also wears a blinded CGM for one week each month and this data will be reviewed as well. We are examining these reports for adverse events and the potential of adverse events (e.g., hypoglycemia). When the control group starts use of CGM non-adjunctively (month 7), they will follow the same pattern of data review that the intervention group did.

3.2. Definition of Adverse Event

Reportable adverse events in this study include any untoward medical occurrence that meets criteria for a serious adverse event or any medical occurrence (expected or unexpected) in a study participant that is study or device-related.

Hypoglycemic events are recorded as adverse events if the event required assistance of another person due to altered consciousness and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

On each daily download (week 1 of non-adjunctive CGM use) and weekly download and review (within the first month), we will also document the percent time spent at or below 60 mg/dL. If this value is greater than or equal to 5% (>1.2 hours per day), we will notify the participant's caregiver and diabetes care provider in order to prevent future hypoglycemia. These criteria will also apply to the CGM data obtained from monthly blinded CGM use in the control group.

Hyperglycemic events are recorded as adverse events if the event involved diabetic ketoacidosis (DKA), as defined by the DCCT, and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones > 1.0 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

Skin irritation from sensor wear will be recorded in specific sections of the case report forms. An adverse event form is only completed if skin irritation is severe.

Distress or discomfort experienced by participants as they complete surveys is not considered an adverse event. However, we have trained psychologists on staff who will be available to address any distress or discomfort and initiate referrals if requested.

3.2. Recording of adverse events

Throughout the course of this study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the participant, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the participant at each visit and phone call and complete all adverse event forms online. The medical monitor will review each adverse event form to verify required coding and reporting.

The study investigator will assess whether an adverse event is related or unrelated to the study by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or by study procedures.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

3.3. Reporting serious or unexpected device-related adverse events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect

3.4. Unanticipated adverse device event

An unanticipated adverse device event is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the coordinating center immediately via completion of the online serious adverse event form.

The principal investigator will notify all participating investigators of any adverse device event that is both serious and unexpected. Notification will be made within 10 days after the PI becomes aware of the event. Such events will be reported to the FDA according to regulatory requirements.

Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

3.5. Data and safety monitoring board

An independent Data and Safety Monitoring Board will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled adverse event data at the completion of the study.

3.6. Potential risks and side effects

Loss of confidentiality is a potential risk, and is protected by the safeguards discussed above. Hypoglycemia, hyperglycemia, and ketone formation are always a risk in subjects with type 1 diabetes. Subjects will be closely monitored for this. When wearing CGM sensors there are risks of skin rashes, allergic reactions to tape, infections at the insertion site, or small pieces of the sensor breaking off or remaining under the skin. These risks will be monitored, but study staff will not oversee insertions, tracking of sensor information, and other diabetes device information.

3.6.1. Lancing risks

A small drop of blood will be obtained by finger stick to measure blood glucose and HbA1c. This is a standard method to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. We recommend children with diabetes check their blood sugar at least 4 times daily. This should not be a significant contributor to risks in this study as finger lancing is part of the usual care for people with diabetes.

3.6.2. Sensor site risks

Whenever the skin is broken there is the possibility of an infection. CGM sensors are inserted under the skin. There may be bleeding where the sensor is inserted, which can cause bruising. CGM site infections occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if a sensor is left in longer than recommended. Participants will be carefully instructed about proper use of sensors.

3.7. Risk of hypoglycemia

There is always a risk of hypoglycemia for patients with insulin-dependent diabetes. The frequency of hypoglycemia during this study is not expected to be greater than the risk incurred during daily living. If severe hypoglycemia occurs, it is readily treated with either oral glucose or glucagon injection. To minimize the risk of hypoglycemia due to "stacking" insulin doses, study participants will be instructed in their initial education (face-to-face and in educational materials) not to take rapid acting insulin injections to correct hyperglycemia more than once every 3 hours. Further, the low glucose alert on the Dexcom G5 system will be set at 70 mg/dl for all participants on CGM.

3.8. Risk of hyperglycemia

Hyperglycemia and ketonemia can occur if insulin delivery is attenuated or suspended for an extended period. This is a risk of type 1 diabetes that is not expected to be greater during the study period than it is during daily living. If severe hyperglycemia occurs, participants will be advised to treat with insulin therapy or to seek medical attention from the child's diabetes care team.

3.9. Other risks

Subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM. If these reactions occur, different adhesives (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Data downloaded from the CGM and the home glucose meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

Psychological and human factors testing and focus groups may make study participants uncomfortable. Subjects are free to withdraw from the study at any time. A psychologist or a health care professional will be available to help them with their stress or anxieties.

3.10. Adequacy of protection against risks

3.10.1. Recruitment and informed consent

All minorities will be encouraged to participate. Economically and educationally disadvantaged people, parents who are employed at the clinical center (Stanford or the University of Colorado) will be eligible to enroll their child in this study if they meet all the study criteria. Subjects will be recruited from our clinics, chart review, and IRB approved patient recruitment lists. We will also use IRB approved recruitment materials to post the study on clinicaltrials.gov and the local universities' research and department websites. Participants may self-select to join the research by responding to advertisements on social media. These posts will provide contact information for the research staff at each site. We will not interact with potential participants or enrolled participants through these media. We will actively work to prevent harm to all subjects enrolled in the study. We will work to avoid coercion by allowing equal enrollment opportunities for employees, as well as non-university affiliated subjects. We will ensure that all families are informed that their participation is voluntary, that they will receive no ill treatment should they decide to not participate, and that they will receive no special advantages, aside from those mentioned in the "benefits" section of the consent, for participating in the study.

Participation will be voluntary and all participants must provide consent prior to inclusion in this research study. The primary investigator at each of the participating clinical sites, or one of their designees, will explain the nature, purpose, expected duration, and risks of study participation to each eligible family. The primary investigator at each site, or one of their designees, will also obtain consent and authorization for the release of personal information.

For children < 18 years of age we will follow the federal guideline 21 CFR 50.52 for clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. In accordance with federal guideline 21 CFR 50.55 we will require that the permission of two parents is required, unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child. After speaking with the subject and their parent and/or legal guardian, questions will be answered about the study, and the participant and/or parent and/or legal guardian will be asked to explain what they understand about the study in order to assess the autonomy of the subject and caregiver and their comprehension of the explanations provided. A copy of the consent form will be provided to the adult subjects or parent or guardian of subjects < 18 years of age, and a copy will be placed in the subject's medical file at the participating institution.

3.10.2. Protections against risk

All protocols and consent documents will be approved by the local IRB at each clinical site.

All of the participating clinical centers have an endocrinologist on call 24/7 for any severe events that should occur. Likewise, a licensed clinical psychologist is available for any concerns on the psychological side. Severe events are not anticipated but will be monitored. Study personnel are always available for questions.

Hyperglycemia and ketone formation are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. Subjects will have blood ketone meters provided through routine clinical care. Insulin can be given as a subcutaneous injection to treat hyperglycemia. Participants will have access to phone numbers for the study physician and endocrinologist on call.

Participants in the intervention group will receive standardized education about CGM and its use after randomization. Participants in the control group who wish to start CGM at six months will receive standardized education about CGM and its use. Both groups will be instructed on inserting and calibrating the sensor. Participants are free to check blood glucose via fingerstick at any time and encouraged to do so if/when the child or parent notices a potential discrepancy between CGM and fingerstick values. A person trained in delivering education about CGM will deliver the education about CGM use and will assist with inserting the first sensor. This individual will be available to assist with questions from participating families. In addition, Dexcom representatives are available to the family for technical questions or issues with the system, just like the access any Dexcom user has.

3.11. Study stopping criteria

Individual subjects will be removed from the study for the following reasons: pregnancy, study-related adverse events (i.e. severe hypoglycemia, loss of consciousness, hypoglycemia related seizure, DKA related to non-adjunctive CGM use or study-related event requiring hospitalization), severe skin infection requiring systemic antibiotics, severe reaction to sensor tape, or other reasons that develop during the study that in the judgment of the investigator make it unadvisable for the subject to continue with the study.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS

4.1. Benefits

It is expected that this protocol will yield knowledge about the impact of continuous glucose monitoring on families with newly diagnosed children with type 1 diabetes. The introduction of CGM in youth with T1D at diagnosis might allay parents' fears, ease their sense of diabetes-related distress and foreboding, and impact glycemic variables measured during the first year of T1D, however there is no guarantee of any benefit from participating in this research study.

4.2. Subject compensation

There will be no cost to the subjects to participate in this research study. Parents will receive $40 for the completion of each of three assessments. Youth 11-17 years of age will receive $25 for the completion of each of three assessments. In total, a family can receive $195 for completion of the study and keep the CGM system. All CGM sensors and required equipment for the protocol will be provided for study participants free of charge.

4.3. Subject withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. For subjects who withdraw, their data will be used up until the time of withdrawal.

4.4. Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. De-identified subject information may also be provided to research sites involved in the study.

4.5. Level of risk

This research proposal in children is consistent with 21 CFR 50.53 - Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

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