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Official Title of the Study:

Use of Continuous Glucose Sensors by Adolescents with Inadequate Glycemic Control

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1. INTRODUCTION TO THE RESUBMISSION

This is a resubmission of R01-DK080831 in response to PA-07-097 "Chronic Illness Self Management in Children and Adolescents". Below, we have outlined responses to each issue raised in the study section's insightful and thorough critique. We have italicized the most substantive changes in the revised text.

The safety of giving continuous glucose sensors (CGS) to adolescents with poor adherence and poor glycemic control was questioned. Adolescents may stop doing finger-stick blood glucose monitoring, they may not calibrate the devices properly and they may make treatment changes based on CGS only rather than finger-stick glucose checks. These human subjects concerns suggest that the proposed study is potentially unsafe and thus unethical. We have addressed these points in multiple ways. The GuardControl trial results [1] show that youths with baseline $HbA_{1C} \geq 8.1\%$ randomized to daily CGS use were treated safely and effectively. Patients who were randomized to the Guardian-RT had mean decrease in HbA_{1C} of 1.0% at 3 months and HbA_{1C} did not increase for controls during the study. Frequency of conventional self monitoring of blood glucose (SMBG) did not decline significantly in either control or CGS patients and remained at 4.6 checks per day at the end of the study, which is above the commonly recommended 4 checks per day. Correspondence from the PI indicates that safety concerns expressed by the study section were not observed in the GuardControl trial. Youths in the two CGS groups had a total of two episodes of severe hypoglycemia, one not during CGS use and one detected by the CGS that did not respond to corrective carbohydrate intake. Diabetic ketoacidosis occurred once in each group. Thus, in a randomized trial enrolling an adolescent sample similar to that proposed here, CGS use decreased HbA_{1C} safely without increasing severe hypoglycemia and it was not associated with significant decreases in the frequency of SMBG. Also, we have summarized the DirecNet studies of the Freestyle Navigator CGS with youths on insulin pump therapy [2] and multiple daily injections. [3-4] These data show that 13 weeks' use of the Navigator decreased mean HbA_{1C} by 0.3% from baseline for insulin pump patients and 0.6% for multiple daily injection patients. When data from only patients with baseline $HbA_{1C} \geq 7.5\%$ were analyzed, decreases in HbA_{1C} were more pronounced (0.5% and 0.8%, respectively). Reportable adverse events were negligible and did not differ among those with baseline $HbA_{1C} \geq 7.5\%$ versus <7.5%. Although SMBG frequency declined somewhat more in the DirecNet studies than in the GuardControl trial, the frequency of conventional SMBG in the DirecNet studies was not correlated with HbA_{1C} or severe hypoglycemia; hence, a decrease in SMBG frequency can occur safely in the context of CGS-augmented therapy. Finally, the Juvenile Diabetes Research Foundation's Artificial Pancreas Project, in which Dr. Wysocki is an investigator, has an external Data Safety Monitoring Board that reviews study performance and adverse events every 6 months. The DSMB met recently now that recruitment has ended (n = 451 patients) and, after more than 1,600 patient-months of CGS use, has recommended the continuation of the trial without any required changes in the study protocol or safety monitoring procedures. The GuardControl and DirecNet studies suggest that CGS use as an adjunct to intensive diabetes management can be both therapeutic and safe when used in patients with previously inadequate glycemic control. Also, an external, independent DSMB for the very large JDRF trial has concluded that use of CGS with youths with T1DM is safe and has sufficient therapeutic promise to warrant continuation of the trial.

In addition to these published data and clinical experience supporting the safety and efficacy of CGS use in teens with suboptimal glycemic control, there are several safeguards that were part of the initial application and others that have been added. First, the study was to be offered only to patients who were already on stable, intensified insulin regimens or who were interested in transitioning to such a regimen from a conventional regimen. In the revision, eligibility is limited to patients already on intensified regimens. Thus, all patients entering the study will have an established intent to achieve excellent glycemic control and enhanced lifestyle flexibility. Second, diabetes education about CGS use will emphasize that CGS is to be used as an adjunct to conventional SMBG and that SMBG checks should be used to verify CGS results before any regimen adjustments are made in response to CGS results. Also, all three of the currently available CGS devices will simply stop operating if the required calibration SMBG checks are not entered during the windows of time required for each device. Hence, youths who do not perform calibrations as required will not be making treatment adjustments or decisions based on CGS data that is flawed due to that type of noncompliance. Third, we have changed the entry criteria to further ensure patient safety. We lowered the minimum HbA_{1C} required for enrollment from 8.0% to 7.5% and imposed a maximum allowable baseline HbA_{1C} of 10.0%. Adolescents will be eligible to enroll only if they have completed an average of 3 or more SMBG tests daily during the preceding 3 months. Fourth, we have planned a "rescue" procedure for any participant whose HbA_{1C} remains above 9% for 2 consecutive visits or whose HbA_{1C} increases by more than 1.0% over

baseline. As would typify clinical practices at the participating sites, this will consist of offering monthly clinic visits with a diabetes nurse, weekly telephone consultation with the nurse and referral to a dietitian, social worker, psychologist or psychiatrist at the discretion of the treating endocrinologist. Fifth, an external Data Safety Committee will carefully monitor the safety of study participants, particularly with respect to the concerns about youths' decreasing the frequency of conventional SMBG to unsafe levels. Finally, CGS sensors will be distributed once each 2 weeks to patients and, if a youth fails to demonstrate an average of at least 3 SMBG checks per day in the intervals between these distributions, no further sensors will be supplied until adequate SMBG frequency has been restored. Together with the promising data on therapeutic efficacy and safety of CGS use discussed above, and these numerous procedural safeguards, we are confident that participants in the proposed trial will enjoy levels of glycemic control and freedom from foreseeable adverse events that are at least as favorable as those experienced by comparable patients who do not enroll in this study.

There is no manual for the Behavior Therapy intervention and no preliminary data supporting its efficacy. This was an important oversight; the initial application did not include adequate detail about the CGS+BT intervention. We have developed and appended a detailed intervention manual that provides an organized conceptual and practical guide to how, within a motivational interviewing framework, we will assess participants' behavioral strengths and weaknesses that may affect therapeutic benefit from the CGS device and how we will select, implement, evaluate and refine an individualized behavior therapy intervention to enable participants to derive the greatest possible benefit from CGS use and to enhance maintenance and generalization of those changes. Our intent was to reflect the best clinical practice of behavior therapy as applied to adolescents' CGS-specific behavioral problems. [5-10] Hence, the approach is intentionally flexible since it will be applied to varied target behaviors in diverse family contexts. At the same time, the intervention is conceptually driven by Behavioral-Family Systems Theory and carefully manualized for dissemination and portability. In fact, all empirically validated behavioral interventions with this population were highly flexible, manualized, theoretically driven interventions. This includes our own Behavioral Family Systems Therapy for Diabetes, [11-16] Ellis, et al.'s Multi-systemic Therapy, [17-18] Gray's Coping Skills intervention, [19] Delamater's Diabetes Self Management Training, [20] Anderson and Laffel's Diabetes Teamwork intervention, [21-22], Nansel et al.'s Diabetes Personal Trainer model [23] and Channon's applications of motivational interviewing to this population. [24-25] Also, Dr. Wysocki is a PI in the multicenter Family Management of Childhood Diabetes trial, which is testing a flexible, individualized family intervention targeting diabetes adherence and problem solving among early teens with T1DM. In all of these trials, intervention targets and methods were negotiated with patients and families to produce an individualized, problem-focused strategy with the patient/family at the center of the treatment team. We have expanded our rationale for the design of the behavioral intervention and the extensive empirical data from multiple research groups that supports the hypothesized efficacy of our approach. Each element of the planned intervention has empirical support with this specific clinical population, either from our own studies or from others' research, except that the targeted behaviors relate specifically to utilization of CGS technology in diabetes management. We are more explicit about this in Sections 3 and 4 of the application and in the intervention manual (See Appendix). We have added Linda C. Sobell Ph.D. as an expert consultant in behavior therapy interventions conducted in a Motivational Interviewing context.

The conceptual basis of the study needs to be articulated more clearly, especially regarding Specific Aims 2 and 3. In Section 3, we added a detailed conceptual framework for the study, placing it in the context of Robin and Foster's integration of Behavioral and Family Systems Theories and devoted substantial space to articulating how the model constructs may affect the optimal use of CGS in diabetes therapy.

Patients currently on conventional regimens would be changed to intensive regimens at enrollment. It is unclear how intervention effects will be disentangled from effects of this change. This is an excellent point. We will enroll only adolescents who have been intensively treated for at least 6 months on either insulin pump or multiple daily injection regimens based on carbohydrate counting and use of insulin dose correction factors. This characterizes about 80-85% of all patients at the three sites and so this change will not appreciably affect the feasibility of the sampling plan.

Skills of the team and family in selection of the CGS device may impact study outcomes. While this concern is legitimate, we believe our planned approach reflects evolving clinical practice in the incorporation of technological advances in diabetes management and is consistent with our objective of evaluating CGS addition to care as it is likely to be practiced clinically. It is unclear how one would measure the proficiency of a team's skills in CGS device selection. Variability in families' pertinent skills will further cloud this picture.

Regardless, there are no pertinent empirical data and no validated measures that would enable us to explore this rigorously. Involvement in the selection of the device with advice and consultation from the medical team tailors CGS use to individual needs, preferences and circumstances and therefore may generate initial and lasting enthusiasm among study participants. Limiting participants' input in CGS device selection would possibly lead to loss of interest and motivation and would depart from what is likely to be standard clinical practice. This aspect of the protocol is consistent with current emphases in chronic disease management such as patient empowerment, [26] autonomy support [27] and motivational interviewing. [28-30] We will train clinical staff involved in this process to encourage a consistent approach. Materials developed in the JDRF Artificial Pancreas Project will be used to assist adolescents, parents and clinicians in the CGS selection process. Stratified randomization should also minimize effects of this potential concern.

Overlapping clinical and research duties may create sources of bias. We have clarified in Section 5 that recruitment of families will be done by diabetes nurses and research assistants who will not deliver the behavioral intervention. The behavioral interventionists will not be involved in data collection. We have added a 30% FTE Research Assistant at each clinical site so that administration of questionnaires and interviews can be segregated effectively from diabetes clinical management and the behavioral intervention.

The design requires a control group for the extra attention to the CGS and CGS+BT groups. We would argue that the "extra attention" given to the CGS and CGS+BT groups is the independent variable in the study and so it is scientifically sound that the control and experimental groups differ on this dimension. The Diabetes Control and Complications Trial, perhaps the most influential diabetes study ever done, did not control for the added attention given to the Intensive Therapy group.

The method of stratified randomization was not specified. We have described in more detail in Section 5 exactly how randomization will be stratified. Patients will be grouped into high and low HbA_{1C} strata ($\geq$ or < 8.8%). Separate randomization lists will be developed and utilized for each center so that patients within each HbA_{1C} stratum will be randomized with equal probabilities to the SMBG, CGS or CGS+BT groups at each center. These features will enhance the likelihood that the three groups will have similar baseline HbA_{1C} and ensure that about one third of participants will be randomized to each group at each center.

The statistical analysis plan lacks detail about the model variables. Possible "site effects" need to be anticipated. The analysis plan has been completely rewritten to correct these deficiencies and our new statistical consultant, Rusan Chen, Ph.D. of Georgetown University has substantial experience in behavioral diabetes research. Neither the DirecNet Navigator, GlucoWatch nor the GuardControl studies revealed significant site effects on primary outcomes and so this concern may be inconsequential. Nonetheless, the revised analysis plan addresses this issue and randomization will be stratified within centers.

Several budgetary and overlap concerns were mentioned. Concerns about the budget being excessive are addressed in the Budget Justification section. The budget is driven largely by costs for personnel, CGS devices and replaceable sensors and these have been justified carefully. We obtained four estimates for central HbA_{1C} lab functions and selected the most economical alternative, Baptist Medical Center in Jacksonville. Other budget reductions have been incorporated, most notably limiting provision of SMBG test strips to participants who lack insurance coverage for them. There is no overlap with the DirecNet studies (which will not focus on continuous glucose sensors as of September, 2007) or the JDRF Artificial Pancreas Trial (which does not include a behavior therapy intervention). Dr. Wysocki is no longer supported by the DirecNet grant and the JDRF trial will conclude before the earliest start date for the research proposed here.

More detail is needed regarding the analysis of cost effectiveness data. We have described exactly how the cost effectiveness data for this secondary objective will be analyzed. We will complete descriptive analyses to estimate and report the incremental costs associated with the CGS and CGS+BT interventions relative to SC and, if there are group differences in the frequencies of emergency room visits or hospitalizations, we will calculate the incremental cost for each such event prevented by the CGS and CGS+BT regimens.

SUMMARY
We believe that we have carefully and thoroughly addressed each concern expressed in the prior critique and that we have submitted a substantially stronger application as a result. We hope that the reviewers concur with this assessment. Substantive changes appear in italics throughout the research plan.

2. SPECIFIC AIMS This revised application responds to NIH Announcement #PA-07-097 "Chronic Illness Self-Management in Children and Adolescents". It addresses the priorities stated in that announcement related to testing interventions targeting improved self-management of pediatric chronic diseases.

Treatment of type 1 diabetes mellitus (T1DM) requires daily insulin injections or use of an insulin pump, self-monitoring of blood glucose (SMBG) several times daily, regulation of carbohydrate intake, regular exercise and correction of hyperglycemia and hypoglycemia. [31] The outcomes of family management of pediatric T1DM reflect many psychosocial influences. [32-35] Some youths and families negotiate these challenges effectively, but others endure poorer glycemic control, treatment adherence, family relations and quality of life during this period. [32-35] Poor adaptation to T1DM in youth may persist into early adulthood, increasing the risks of long-term complications. [36-37] Practical methods are needed to enhance the capacity of youths and parents to manage T1DM effectively. Continuous glucose sensors (CGS) have now been developed that provide continuous real-time data on glucose levels and trends. The CGS could benefit many adolescents with T1DM by providing more useful feedback on glycemic levels, direction and variability than is feasible with conventional SMBG. [38-43] But, these benefits may depend on how well families can collaborate in using CGS data for therapeutic decision-making. [44-45] While youths in sub-optimal glycemic control could benefit from CGS, the benefits could be enhanced if they received a specific, targeted behavioral intervention. Drawing on our prior studies, the proposed research will explore whether glucose regulation by youths with T1DM using CGS can be enhanced by a behavioral intervention targeting diabetes management behaviors of adolescents and parents/caregivers that are critical to effective CGS use. This application addresses these specific aims:

SPECIFIC AIM 1. In a 3-center sample of 150 adolescents with T1DM and HbA$_{1C}$ of 7.5% to 10.0%, we will compare the effects of Standard Care (SC) alone or augmented by either CGS alone (CGS) or CGS plus a behavior therapy intervention designed to optimize CGS benefits (CGS+BT). Primary outcome measures will be HbA$_{1C}$, 7-day continuous glucose profiles, and indices of blood glucose variability and risks for severe hypoglycemia. Frequency of severe and moderately severe hypoglycemia will be secondary outcomes.
SPECIFIC AIM 2. The study will determine if and how adding the behavioral intervention to accepted clinical and educational practices related to CGS use affects diabetes treatment adherence, parent-adolescent teamwork, satisfaction with CGS use, quality of life, and family communication about diabetes management.
SPECIFIC AIM 3. The proposed work will evaluate mediating and moderating effects of certain demographic variables and diabetes-specific behaviors of adolescents and parents that are suggested by theory or related empirical research as likely to affect benefits realized from CGS use.

3. BACKGROUND AND SIGNIFICANCE
3.1. Evolution of diabetes management since the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial (DCCT) proved that maintenance of near-normoglycemia reduced the onset and progression of long-term complications. [46-48] DCCT adults had lower HbA$_{1C}$ than did participating youths, but the form of treatment effects and associations between HbA$_{1C}$ and complication rates were similar. Our NIH-funded trial of Intensive Therapy versus Usual Care for youths with T1DM explored prediction of benefit from these regimens. Our study [49-51] and another [52] suggest that intensive therapy is safe and effective with adolescents with T1DM and that it can improve glycemic control without appreciable adverse effects. Unfortunately, a minority of adolescents today maintain HbA$_{1C} \leq$ 7.5%, the American Diabetes Association's recommended target [53] ($\leq$ 7.0% if considered safe by the physician). Although there has been substantial improvement in the management of T1DM in adolescence in the past few decades, much room for improvement remains. Continuous glucose sensors could enable additional therapeutic benefits.

3.2. Continuous Glucose Sensors: Medical, Educational and Psychological Context. So-called "continuous glucose sensors" (CGS) yield near-continuous glucose feedback automatically and with minimal discomfort. Various devices have been tested [54-58] and several are FDA-approved as adjuncts to SMBG in T1DM regimens. The accuracy of these devices is adequate compared to laboratory assays [59-62] and their provision of 24-hour glucose profiles and detection of glycemic trends are not feasible with conventional SMBG. Existing CGS devices will be refined and new ones will emerge. [63-67] CGS use could change T1DM care greatly, with major increases in the breadth and amount of glucose data, and timely feedback about the glycemic effects of treatment events and thus yield many benefits. [1-4, 38-43, 68] CGS use could enable reduced HbA$_{1C}$, glycemic variability, and severe hypoglycemia. Improved detection of previously unrecognized glycemic patterns could guide treatment adjustments. CGS feedback could reinforce educational concepts and possibly reduce health care costs. By revealing more saliently the effects of non-adherence, some

patients may be motivated to comply more consistently. CGS could enhance clinicians' refinement of youths' diabetes problem solving, helping them to develop more self-confidence in their self-care skills. Parents and teens could develop a proactive, rather than reactive, approach to managing diabetes, achieving more lifestyle flexibility. Based on experience in the CGS studies described below, CGS became an integral part of T1DM care for about 75-80% of youths who tried it. But this estimate is based on samples of highly selected, well-motivated and younger children and it may not pertain to adolescents with suboptimal glycemic control.

But some youths and families may not benefit from CGS use since it increases the care burden and introduces new self-care demands. [42, 44-45] Some youths and parents may have unrealistic expectations about what CGS can achieve and be easily discouraged by slow improvement. Many youths might view CGS as a threat to their privacy and autonomy. The amount of CGS data may be overwhelming and highly anxious individuals may over-react to CGS feedback by over-correcting momentary glucose fluctuations. Wearing the CGS increases the salience of diabetes to peers, possibly increasing social stigma and unwanted intrusions of diabetes into one's social life. Access to CGS data may aggravate teen-parent conflict over unwanted glucose excursions or cause guilt when preventable problems are not recognized. Research on the adoption of this technology should include plans to analyze possible unwanted effects of CGS use.

Outcomes from medical advances such as use of CGS may depend on psychological variables. [42, 44-45] Previous research identified many psychosocial variables that influence T1DM outcomes and we will measure those that have yielded the most robust associations. [32-35] Key demographic factors are: child age, pubertal stage, parents' marital status, socioeconomic status, race/ethnicity and family composition. [69-72] Psychological characteristics of individuals associated with T1DM outcomes are: child or parent psychological adjustment, [73-74,] diabetes knowledge and problem-solving, [75-80] treatment adherence, [81-83] fear of hypoglycemia, [84-85] attitudes toward SMBG, [79-80] and stress and coping. [86-87] Family variables that influence T1DM outcomes are family function, [88-89] family sharing of T1DM responsibilities, [90-96] and diabetes-related conflict. [97-98] These variables will be measured throughout this study to clarify their effects on glycemic outcomes. We will evaluate both moderation and mediation of therapeutic benefit from CGS use with appropriate analyses of the contributions of such variables to treatment effects on the primary outcomes.

3.3. Available CGS devices. Dr. Wysocki has been involved since 2001 in studies of the accuracy and clinical use of CGS. [2-4, 45, 56-57, 59, 61-62] Three CGS devices either have FDA-approval for use in adults or approval is expected soon. These are the Guardian RT/Paradigm (Medtronic-Minimed, Inc.), the Freestyle Navigator (Abbott Laboratories) and DexCom 7 (DexCom, Inc.). Features of these devices are shown here, and links to current product information websites are in the appendix.

Table 1. Comparison of features of currently available continuous glucose sensors.

	Navigator	DexCom 7	Paradigm/Guardian
Range of glucose values	20 to 500 mg/dL	40 to 400 mg/dL	40 to 400 mg/dL
Frequency of glucose values	Every minute (saved every 10 minutes)	Every 5 minutes	Every 5 minutes
Lifespan of sensor	120 hours	168 hours	72 hours
Warm up period	10 hours	2 hours	2 hours
Calibration frequency	4 times at ~10, 12, 24 and 72 hours after sensor insertion	2 times a day (every 12hrs)	2 times a day (every 12hrs)
SMBG Meter for Calibration	FreeStyle (built in)	One Touch Ultra (connected via a cable)	BD Logic (connected via radiofrequency); can also enter manual calibrations from any HGM
Alarms	Hypo, hyper (adjustable) Predicted alarms based on rate of change	Hypo, hyper (adjustable) No predicted alarms	Hypo, hyper (adjustable) No predicted alarms
Trend Arrows Displayed	Yes	No	Yes
Memory capacity	Max. 60 days of glucose readings	Max. 30 days of glucose readings	Max. 90 days of glucose readings
Entering of events	Insulin, meals, exercise, health, other	Not available	Insulin, meals, exercise
Other features	Sensor is waterproof	Sensor is waterproof	Can be combined with a Medtronic pump in a single device (functioning separately)
FDA approval status	Pending for adults	Approved for >=18 year olds as adjunct to SMBG	Approved for children and adults as adjunct to SMBG

Other CGS's will emerge and the proposed study will use the most advanced devices at the time this work begins. If any device selected for this study does not have FDA approval by the start date, an IDE will be sought for its use. The current devices all measure glucose in interstitial fluid using indwelling electro-chemical sensors to yield time-averaged estimates derived from the electronic "signature" of glucose molecules. The various sensors are designed for 3 to 7 days' use. All yield nearly continuous glucose profiles, but there is a

physiological lag of 10-15 minutes between glucose levels in blood versus the interstitium. Each device gives feedback on estimated interstitial glucose levels over brief (e.g. 5-min) intervals and alarms notify the user of out of range glucose values or of rapid glycemic changes. All require entry of SMBG tests for calibration at varied intervals. All of the devices can be downloaded to a computer, although the analytic options vary. The Medtronic-Minimed Paradigm CGMS is integrated within an insulin pump housing, but the infusion of insulin is not directly regulated by the CGS glucose data. The Medtronic-Minimed Guardian-RT is the same CGS device but it is not incorporated into an insulin pump. Insulin infusion via pumps may some day be driven by CGS glucose data, but that development is probably several years in the future. [68, 99, 100] We will offer to participants the CGS devices that offer the greatest accuracy, convenience, safety and reliability when the study begins.

It is difficult to compare the accuracy of CGS devices to methods yielding point-in-time glucose estimates. [101-102] CGS accuracy has improved steadily and now rivals the accuracy of SMBG meters, while enabling detection of glycemic trends that is not feasible with SMBG. Current CGS devices tend to blunt rapid or extreme glycemic changes, [56-57] but they may still detect fluctuations that are missed by SMBG. The current CGS devices, while imperfect, may be accurate enough to enable more timely decision-making and glycemic benefits. Consultant mathematician Boris Kovatchev, Ph.D. is a leading expert on quantifying the accuracy of CGS devices and analyzing glucose dynamics using SMBG and CGS data. Dr. Kovatchev will bring his expertise to this study, continuing his work on prediction and quantification of glycemic variability. [102-113]

Comparing available CGS devices is not an aim of this application. The protocol is intended to reflect best clinical practice in adding CGS to T1DM care. This includes evaluating the patient's needs and characteristics, considering the pros and cons of the CGS options for that youth and, with the family, selecting the "best-fitting" CGS device. The proposed study will evaluate benefit from CGS use that is initiated in this way. Each enrolled youth will consult with his or her parent(s) and diabetes team to select the best CGS device for that patient.

3.4. Cost effectiveness analysis. Cost-effectiveness analysis (CEA) quantifies the added value of medical advances. After ascertaining all costs of each intervention, optimal CEA methods yield an Incremental Cost Effectiveness Ratio (ICER). [114-116] This requires calculation of Quality-Adjusted Life Years based on health utilities measures (e.g. treatment utilities, experienced utilities, complications utilities, willingness to pay). [114] Utilities measures often employ "time-tradeoff" questions asking respondents to indicate how many years in their current health state they would be willing to trade for a given health outcome. [114] Many youths may struggle with these abstractions, the methods have not been studied with pediatric diseases and parental proxy for youths' responses has not been validated. A simpler, more affordable approach to cost effectiveness analysis is proposed here. During four selected 2-week periods, all clinicians treating adolescents in this study will record their time devoted to delivery of each adolescent's care, not including time specifically for research tasks. Methods used successfully in Dr. Wysocki's prior trial of intensive therapy [45-46] will be used in this study. Key drivers of health care costs will be recorded systematically, including hospitalizations, emergency room visits and clinic visits. The collection of these data will permit a basic assessment of the relative costs and therapeutic benefits from CGS use with and without a behavioral intervention relative to standard care and of possible cost savings due to CGS use through reduced health care utilization compared with standard care.

3.5. Conceptual model. From the perspective of behavior theory and applied behavior analysis, CGS use could yield both therapeutic and contratherapeutic behavioral effects in youths with suboptimal HbA$_{1C}$. Family systems theory implies that adding CGS to T1DM care could affect, and be affected by, all elements of the family system. CGS could yield benefits that SMBG cannot provide, permitting more informed decisions about insulin dosing, eating and exercise, allowing patients to anticipate and prevent glycemic excursions, reduce glycemic variability and achieve normoglycemia more often. Also, CGS can illustrate the glycemic effects of events such as overeating, over-exertion, and missed or delayed insulin injections. If CGS data are used carefully to guide T1DM care, youths may enjoy better short-term outcomes, more flexible lifestyle, and more meticulous adherence. If these changes reduce the burdens of living with diabetes, youths may also enjoy improved quality of life and family relations. To the extent that behaviors entailed in optimal CGS use yield positive consequences rather than aversive consequences (direct effects on glycemic control or indirect social effects), these optimal behaviors may be strengthened and maintained.

But, adding CGS may entail complications that could counteract these benefits. CGS may compound the burden of T1DM self-care since it must be checked, cleaned, stored, calibrated, safeguarded and explained to others. Use of the CGS in school and some recreational activities may be difficult or impossible. The CGS compounds the complexity of blood glucose data, increasing the frequency of events requiring remediation.

Youths may be confused when CGS values differ from SMBG results or from "expected" values. Alarms signaling unwanted glucose fluctuations may intrude into activities that teens are unwilling to interrupt. False alarms, especially if repetitive, may induce adolescents to disregard the alarms. For teens whose self-care behaviors are inconsistent, their CGS results may also seem capricious, making it difficult to adjust the regimen effectively. CGS feedback could aggravate conflict between youths and parents about glycemic control. Hence, these potential "response costs" from CGS use may undermine its potential benefits. While CGS carries potential benefits, the above concerns suggest that incorporation of CGS into T1DM care may place a premium on family characteristics that influence the effectiveness of diabetes management.

In our prior studies of the GlucoWatch and Navigator, frequency of use of both devices declined steadily over time. The best estimates of frequency of use are from our Navigator pilot studies (See Section 4). Insulin pump patients used the Navigator for about 149 hours per week (88% of maximal) in the first 4 weeks, but this declined to 134 hours per week during the last 4 weeks of the 13 week study (80% of maximal). Children on MDI therapy used the Navigator slightly more often initially (153 hours/week) but declined more rapidly to 109 hours per week (65% of maximal) by the last 4 weeks. Given that MDI patients have actively decided against the use of one T1DM device (insulin pump) it is not surprising that they would be somewhat less enthusiastic than pump patients about use of CGS. Since we plan to enroll youths with suboptimal glycemic control and follow them longer, frequency of CGS use may decline more rapidly and to lower levels in this study. Thus, there are many behavioral variables that may impact effective use of CGS technology. Teens who are already struggling with T1DM management may be at the highest risk of counterproductive behavioral reactions to CGS use. Yet, these same youths could also derive the most therapeutic benefits from CGS if these impediments can be anticipated and prevented and if more positive and constructive behaviors can be encouraged. The behavioral intervention proposed for this study is designed to achieve these effects.

Various counter-productive behaviors of adolescents or parents could impede benefit from CGS use. Also, there are certain behaviors that could promote benefit from CGS use. Targets of intervention in the proposed study will include these "negative" behaviors: Inadequate frequency of CGS use, Resistance to completing calibration SMBG checks, Ignoring alarms warning of impending hypoglycemia or hyperglycemia, Resistance to completing finger-stick BG checks when CGS readings seem inaccurate, Adolescent concern about parental "snooping" or inordinate family attention to glucose levels, and arguments about BG levels. The intervention will also seek to promote "positive" behaviors such as: Problem solving to prevent unwanted BG fluctuations, Parent-youth teamwork and brainstorming around CGS results, Goal setting for improved BG control, Conducting "experiments" to measure effects of exercise changes, etc. on BG levels and trends, Improving family communication about out of range BG levels, Parent-youth negotiation about diabetes goals, responsibilities, etc. Other positive and negative target behaviors will likely emerge as the study proceeds.

The proposed intervention is based on a conceptual model adapted from Robin & Foster's Behavioral Family Systems theory that Dr. Wysocki has explored in his prior NIH-funded trials. [117] While Robin and Foster developed their model for the prediction of the frequency and intensity of parent-adolescent conflict, we have adapted it for the prediction of therapeutic benefit from clinical use of CGS technology in the management of T1DM in adolescents. We contend that the same processes that mediate and moderate parent-adolescent conflict will influence the family's capacity to work together cooperatively to derive benefit from CGS use. Specifically, the model asserts that the degree of CGS benefit achieved by families of adolescents with T1DM is a function of several interactive behavioral characteristics of the family:

- *Characteristics of the family system that provides the social context for T1DM care. [22, 32,69-74,87, 90-91, 94-96]*
- *Family problem solving and communication skills related to diabetes management. [75-80, 92, 95, 98]*
- *Cognitive distortions held by parents and adolescents about T1DM and its management [11-13, 84, 85, 88, 89, 130]*
  (Citations inserted above are T1DM studies that offer empirical support for these relationships)

A diagram of this conceptual model appears below, followed by discussion of how these constructs are thought to operate in the context of CGS-augmented diabetes management. The fundamental tenet of the model is that families are interconnected systems such that perturbations affecting one element of the system are likely to influence other elements of the system. Family members exert reciprocal influences on the contingencies of reinforcement and punishment that prevail upon one another's behaviors. Adolescence is a period that challenges these prevailing contingencies of reinforcement and punishment and that stresses the family's organization of power, influence and decision-making.

Robin and Foster integrated the molar perspective of Family Systems Theory with several principles derived from Behavioral and Social Learning Theories that offer a more molecular perspective of the processes and mechanisms that may govern how families adapt, successfully or not, to the demands of adolescence. They argue that three 'molecular" characteristics determine the degree to which families adapt successfully to the challenges of adolescence, and this application asserts that these characteristics will affect families' capacity to benefit from use of CGS in diabetes care. These characteristics are effectiveness of family communication skills, effectiveness of family problem solving skills and the degree to which family members have distorted cognitions or beliefs about each other's behavior. Robin and Foster summarized an extensive literature on the developmental psychology and family psychology of adolescence and identified variables that differentiate distressed from non-distressed families. Non-distressed families are better able to communicate openly and directly with their adolescents to negotiate disagreements, resolve conflicts and solve problems. Non-distressed families of adolescents are less likely to demonstrate distorted cognitions regarding the behaviors, attitudes and motives of other family members. These distorted cognitions are logical errors that tend to inflame, divert, obfuscate or stop conversation such as overgeneralization, exaggeration, selective abstraction, arbitrary inference, dichotomous reasoning, perfectionism, ruination, insistence on fairness, insistence on autonomy, and inference of malicious intent. In this model, families who have deficient communication and problem solving skills and whose thoughts about each other and about diabetes management are heavily laden with cognitive distortions such as these, are unlikely to exhibit the kinds of family interactions that are conducive to optimal therapeutic benefit from CGS use in diabetes management.
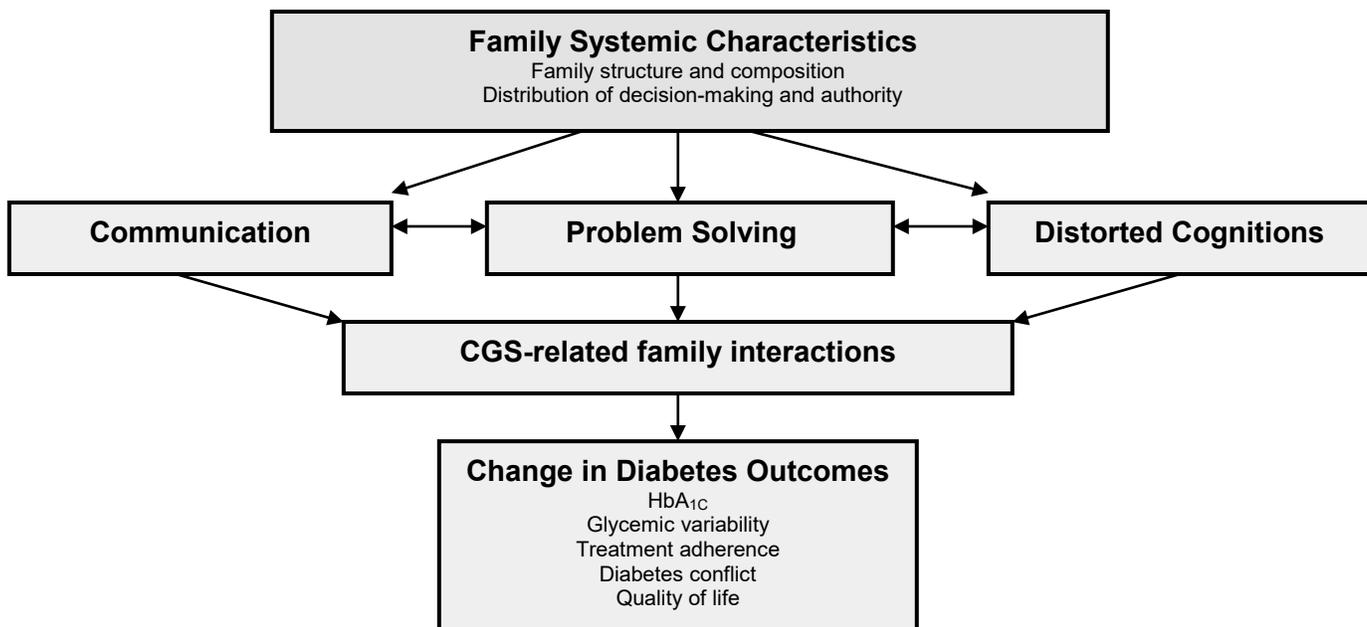
Robin and Foster's Behavioral Family Systems Theory [117] asserts that the interactive behaviors of family members exert reinforcing or punishing consequences upon one another's behaviors and that the development and maintenance of cooperative family problem solving depend on the occurrence of interactions that specifically set the occasion for and reinforce those behaviors. A molecular perspective of CGS-related family interactions suggests that specification, analysis and remediation of the family's implicit contingencies of reinforcement and punishment could enable behavior change specialists to promote family environments that enhance benefit from adding CGS to T1DM care. Use of CGS to improve glycemic control among youths with T1DM requires a family environment that is rich in parental supportive involvement, exhibits healthy and open communication about diabetes and that encourages parent-adolescent cooperative problem solving without exacerbating developmentally typical conflict between teens and adults. Family systems that have anomalous distributions of decision making and influence (e.g. weak parental coalitions, cross-generational coalitions, or triangulation) [117] often demonstrate major difficulties in the domains of family communication, cooperative problem solving and conflict resolution. For example, adolescents whose parents have widely discordant attitudes about the benefits of tight glycemic control may "seek protection" from the more lenient parent when glycemic control is poor. Frequent expressions of distorted cognitions such as those above, often inflame emotions and "de-rail" conversations, and so impede family communication and problem solving. For example, adolescents whose parents over-react to transient glucose fluctuations with angst and foreboding may be

disinclined to further CGS use. Families who lack effective communication and problem solving skills may have difficulty cooperating to respond appropriately to CGS use and the resulting data. For example, families who frequently interrupt one another, change topics of conversation, bring up past failures, or engage in frequent blaming may find it difficult to reach consensus about responding to CGS results and thus miss opportunities to improve the adolescent's glycemic control. To further illustrate the behavioral mechanisms and processes that could be targeted for intervention in the proposed study, the table below lists key interactive behaviors of families of adolescents with T1DM that the model predicts will be important determinants of benefits from CGS use. Therapists who will implement the planned intervention will be trained to identify these characteristics clinically and to target encouragement of these positive behaviors in their treatment plans.

Family behavioral characteristics that may enhance benefit from adding CGS to diabetes management:

- *There is greater emphasis on praise and positive reinforcement than on punishment and criticism.*
- *Family members display positive reciprocity and absence of coercive family processes.*
- *Blood glucose fluctuations serve as a cue for problem solving discussions rather than arguments.*
- *Parental withdrawal from diabetes management is gradual, stepwise, and experimental.*
- *Increased adolescent responsibility precedes parental withdrawal from diabetes management.*
- *Parents are willing and able to resume more involvement in diabetes management if necessary.*
- *Parental withdrawal from T1DM care is goal-directed rather than due to burnout, avoidance of conflict, etc.*
- *Parents monitor and are aware of youths' T1DM management behaviors when away from home.*
- *Parents engage in diabetes problem solving with, rather than for, the adolescent.*
- *There is frequent, effective family communication about T1DM and clear accountability for management tasks.*
- *Parents maintain involvement as a resource or advisor with minimal parent-adolescent conflict*
- *Adolescent often displays self-disclosure about coping with T1DM.*
- *Parental concern about T1DM self-management is expressed lovingly rather than in anger or frustration.*
- *Constructive social supports for T1DM self-care are available from other family members, siblings, and peers.*
- *Recurring problems mobilize more intensive or diverse family problem solving efforts.*
- *Parents advocate for effective diabetes management in school and other such settings.*

3.6. Pertinent behavioral interventions. Many studies affirm the merits of brief behavioral interventions targeting family management of T1DM. [11-25, 118-131] These include trials of behavior modification and behavioral contracting, [121-125] coping skills training, [19, 126-128] peer group and multifamily group interventions, [11-18, 118-119, 129-130] family teamwork interventions, [21-22] and other family approaches. [131] Motivational Interviewing has shown promise with youths with T1DM [23-26] and other adolescent issues. [132-135] Key components of the latter approach are expressions of empathy, development of a discrepancy between the patient's present behavior and important goals or values, and support for self-efficacy and patient autonomy. Motivational Interviewing, rather than being an intervention itself, offers a fertile context for the negotiated development of a patient-centered intervention that is particularly useful with individuals who are resistant to change. We have designed our intervention to include the key ingredients of effective, brief behavioral interventions and to reflect best clinical practices in the application of these tools to enhance family management of T1DM in adolescence.
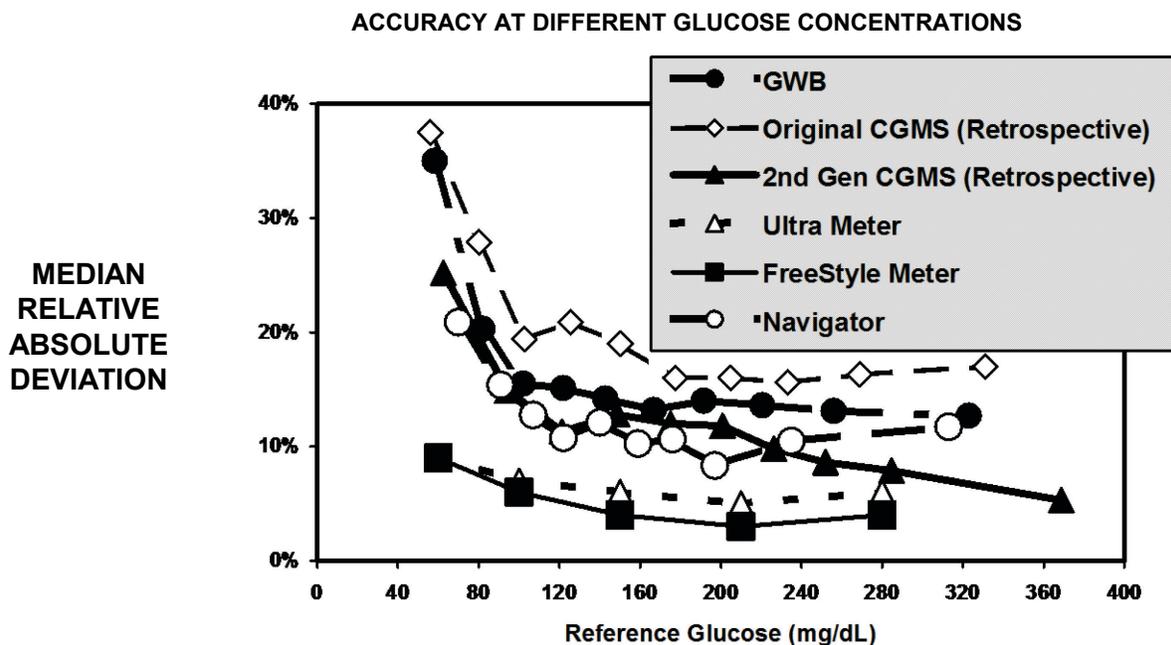
3.7. Safety and efficacy of CGS use by adolescents with T1DM. *Three recent studies affirm the safety and efficacy of CGS use in teens with T1DM. All three showed that augmenting conventional SMBG with CGS use yielded modest, but lasting reductions in HbA_{1C} and glycemic variability. The GuardControl trial [1] randomized 81 youths and 81 adults with HbA_{1C} > 8.0% to SMBG, 3 days' bi-weekly CGS use or continuous CGS use. At 3 months, the continuous CGS group achieved a mean 1.0% reduction in HbA_{1C} compared with 0.6% for the bi-weekly CGS group and 0.3% for the SMBG group. More evidence of the safety and efficacy of CGS in this population was obtained in the Diabetes Research in Children Network's 13-week pilot studies of the Abbott Freestyle Navigator CGS in youths with T1DM on insulin pump (CSII) and multiple daily injection (MDI) regimens described in Section 4.2. [2-4] None of these studies yielded increased frequencies of severe hypoglycemia or diabetic ketoacidosis during CGS use. In all of the studies, frequency of SMBG declined during CGS use, but this was not associated with adverse events. These studies show that CGS use in pediatrics is safe and may yield modest glycemic benefits, even if SMBG frequency declines while it is used. Coupled with the extensive safeguards that are described in Section 5, participation in this clinical trial is likely to result in fewer adverse events among participants than among similar patients who do not enter the study.*

4. PRELIMINARY STUDIES AND PROGRESS REPORT

4.1. Qualifications of the study team. Dr. Wysocki has 1.) Served as the only non-MD PI in the NIH-funded Diabetes Research in Children Network and the Juvenile Diabetes Research Foundation Artificial Pancreas Project. Both networks have conducted CGS studies as described below; 2.) Served as PI on 4 NIH-funded multi-center studies of youths with T1DM, including trials of behavioral interventions and an analysis of prediction of benefit from intensive therapy; and 3.) Published extensively on SMBG and CGS (See Section 7).

Dr. Wysocki has enlisted as co-investigators the Division Chiefs for Pediatric Endocrinology at the Nemours Children's Clinics in Orlando, (Jorge Daaboul, M.D.) Pensacola, (Mark Kummer, M.D.) and Wilmington, Delaware (Grafton Reeves, M.D.). Kimberley Englert, R.N, who has been the Nemours coordinator for several CGS studies, will train nurses at the other sites on the CGS devices and consult regarding education and counseling methods that were effective in those trials. Nemours Children's Clinic-Jacksonville will be the Coordinating Center. Dr. Wysocki has extensive experience with multi-center studies structured in this way, including four NIH grants and service as a PI in the JDRF Artificial Pancreas Project. Coordinating centers for these studies managed enrollment, randomization, data management and statistical analysis while clinical sites recruited participants, obtained informed consent, implemented study protocols, collected data and sent it to the coordinating center. Dr. Wysocki's team has been the coordinating center for several major grants and he has learned other coordinating centers' practices through the multi-site studies described below. These experiences have equipped him to manage the proposed study using a similar organizational structure. Boris Kovatchev, Ph.D. of the University of Virginia brings an international reputation as a quantitative researcher on glucose dynamics, quantification of accuracy of continuous glucose sensors, mathematical models of glycemic variability and prediction of extreme glycemic excursions. His contributions will capitalize on the extensive CGS and SMBG data that will be collected. Rusan Chen, Ph.D. of Georgetown University will be the statistician. He has substantial experience in this role in behavioral research in pediatric diabetes and has special expertise in the use of the Individual Growth Modeling methods that are central to the proposed analysis plan. Linda C. Sobell, Ph.D. will provide expert consultation on integrating motivational interviewing with behavior therapy.

4.2 Diabetes Research in Children Network (DirecNet; 1-U10-HD/DK-41918). A 2001 RFA sought applications for studies of the pediatric use of CGS's. Dr. Wysocki's application, "Continuous Glucose Sensors in Youth: Biobehavioral Study", sought to identify predictors of benefit from CGS use. His application was funded and he became a member of the DirecNet Steering Committee along with 4 physician PI's and this group has since conducted multiple CGS studies. Dr. Wysocki has published on psychological aspects of CGS use, [45] measurement of satisfaction with CGS [57] and methods of quantifying CGS measurement error. [101] Initial DirecNet studies tested the accuracy of two early CGS devices, the GlucoWatch Biographer (GWB) and Medtronic-Minimed CGMS during stable, rapidly decreasing and rapidly increasing glucose levels in youths during 24-hour hospital stays. [59, 62] Point estimates of glycemia by both devices were adequate during the

ACCURACY AT DIFFERENT GLUCOSE CONCENTRATIONS

Legend:
- GWB
- Original CGMS (Retrospective)
- 2nd Gen CGMS (Retrospective)
- Ultra Meter
- FreeStyle Meter
- Navigator

Y-axis: MEDIAN RELATIVE ABSOLUTE DEVIATION
X-axis: Reference Glucose (mg/dL)

steady-state but both devices underestimated rapidly changing glycemia. Both devices detected glycemic trends accurately, implying that adding them to T1DM therapy could be beneficial. The figure above shows the improvements in accuracy of these devices, but both remain less accurate than SMBG meters in terms of point estimates of glucose. All tested CGS devices overestimate very low glucose levels. Manufacturing changes for the CGMS sensors improved accuracy compared with the original CGMS. The figure above portrays the Median Relative Absolute Deviation between CGS devices and SMBG meters compared to readings with the Beckman Glucose Analyzer. This figure compares three CGS devices, the GlucoWatch Biographer (GWB), the first and second generation Minimed CGMS, and the Freestyle Navigator and the Ultra and the Freestyle SMBG meters. The results show that the successive iterations of CGS devices have shown steadily improved accuracy. While CGS accuracy for point estimates of glucose levels lags behind that of SMBG meters, its detection of trends and potential for prevention of extreme fluctuations warrants optimism for its clinical utility.

DirecNet completed a randomized, controlled trial of the GlucoWatch Biographer (GWB), with HbA$_{1C}$ and "blinded" use of the Medtronic CGMS as primary outcomes. [56] A sample of 200 highly motivated, compliant T1DM patients with mean baseline HbA$_{1C}$ of 7.9% was randomized to SMBG alone or augmented with GWB use for 6 months. The study showed that the GWB did not affect glycemic control, hypoglycemia, quality of life, or adherence. GWB use declined steadily and 26% of patients stopped using it. Skin problems, gaps in data, inaccuracy, and calibration failures limited benefit from the device.

DirecNet also evaluated the accuracy of the Freestyle Navigator [62] and completed pilot studies of its clinical utility among 30 youths with T1DM on insulin pumps [2] and 27 youths on multiple daily injections. [3-4] Complete data are available for 13 weeks' use of the Navigator for 51 of the 57 children who enrolled. A total of 9 patients stopped using the Navigator within 13 weeks, 2 on insulin pumps and 7 on MDI regimens. Mean HbA$_{1C}$ declined significantly for pump patients ($p < .01$) and for MDI patients ($p < .04$) over 13 weeks, with larger decreases among patients with higher baseline HbA$_{1C}$ on either regimen. Further slight decreases in HbA$_{1C}$ have been observed among the patients who have continued using the Navigator for up to 18 months. *There was no change in the frequency of severe hypoglycemia relative to the 6 months prior to enrollment for either sub-sample, showing that reduction in HbA$_{1C}$ was not accompanied by increased risk of severe hypoglycemia. Scores on the Continuous Glucose Monitor Satisfaction Scale were uniformly positive for both pump and MDI participants.* Among pump patients, the added Navigator burden did not adversely affect quality of life for parents or children. Youths on MDI regimens, but not their parents, reported significantly improved scores on the PedsQL Diabetes Module [136] after 13 weeks of CGS use. All of these results should be interpreted in context, since the enrolled children and parents were carefully selected and highly motivated and may not be representative of the broader clinical population.

A 2006 RFA to renew this network sought applications focusing on hypoglycemia rather than CGS. Dr. Wysocki transferred his role as a DirecNet PI to his colleague, Nelly Mauras, M.D. to maintain his interests in CGS use by pursuing the study proposed here. Dr. Wysocki's service as a DirecNet PI over the past 6 years provided him with extensive multidisciplinary experience, detailed knowledge regarding available and emerging CGS devices, thorough understanding of the measurement and analytic issues that are unique to CGS evaluations and healthy skepticism and curiosity about the clinical adoption of this technology. He has also developed and validated several measures proposed for collection in this study.

4.3. Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Project

The 5 DirecNet centers are among the 9 clinical sites for this JDRF-funded trial comparing CGS and SMBG regimens in T1DM. Dr. Wysocki is the Nemours' PI. Recruitment occurred from January to December, 2007 and a diverse sample of 451 patients has been randomized to SMBG or to CGS for 6 months; all patients will be offered CGS for the succeeding 6 months. Glycemic control, severe hypoglycemia, health care use, satisfaction with CGS, fear of hypoglycemia, quality of life, and health utilities will be measured periodically. Many aspects of this protocol were integrated into the present application, including: Patient/family selection of preferred CGS device; Clinical use of one of three CGS devices proposed for this study; Continuation Phase with CGS offered as an enrollment incentive; Collection of several of the same measures for evaluating impact of CGS on diabetes care and family life; and Incorporation of periodic 7-day use of a "blinded" CGS device by the SMBG group for comparisons of their glucose profiles to those of the two CGS groups. While working on the JDRF Artificial Pancreas Project, Dr. Wysocki has gained further experience within a large scale, multidisciplinary trial of CGS use in pediatric diabetes. This project also provided psychometric validation data for the Glucose Monitoring System Rating Survey that will be used in the proposed study.

4.3. Family Management of Childhood Diabetes (NICHD Research Contract # N01-HD-4-3361). Dr. Wysocki is one of four PI's for this NICHD research contract. Applications were sought to design and conduct this randomized trial of a low-intensity, family-focused, clinic-integrated behavioral intervention. The intervention seeks to prevent deterioration in glycemic control, treatment adherence, family relations and quality of life in early adolescence. The conceptual framework is that modest behavior change in most families could yield substantial public health benefits. To enhance clinical translation, the interventionists are B.A. and M.A.-prepared persons and the intervention has been manualized. Numerous behavior change handouts have been prepared and refined to address common diabetes-specific behavioral problems. A 9-month pilot and feasibility study of 122 families affirmed the feasibility of the recruitment, retention, measurement and intervention protocols for the study and enabled refinement of the intervention. Subsequently, 410 families enrolled in the main trial, with 94% retention to date over 9 months. Data collection will end in the fall of 2008. Many aspects of this protocol have been incorporated into the present application, particularly an intervention manual, educational materials, behavior management handouts, behavioral homework assignments, and attention to practicality for clinical translation. The primary implication of the FMOD trial for this application is that the PI has gained substantial experience developing, implementing and evaluating a family-focused, clinic-integrated behavioral intervention targeting more effective family management of T1DM in early adolescence. These experiences directly informed the structure and process of the proposed intervention.

4.4. Behavior Therapy for Families of Diabetic Adolescents (1-R01-DK-43802). Dr. Wysocki was also PI on this NIH-funded multi-center trial that has completed its second funding cycle. During the first funding cycle, BFST yielded improved parent-adolescent relationships and reduced family conflict about diabetes, but these changes did not yield corresponding improvements in treatment adherence or glycemic control. [11-13] In the second funding cycle, the BFST intervention was revised to enhance its impact on diabetes outcomes. A sample of 104 adolescents with $HbA_{1C} \geq 8.0\%$ enrolled at Nemours Children's Clinic and at Washington University School of Medicine. Families were randomized to Standard Care alone or augmented by 6 months' treatment either in a multifamily educational support group or in Behavioral Family Systems Therapy. The revised intervention exerted substantially greater effects on adherence and glycemic control, particularly among youths with HbA_{1C} above 9.0%. The revised BFST-D yielded durable improvements in adherence and glycemic control clearly relative to the Standard Care group and more equivocally relative to the Educational Support group, and similar effects occurred on measures of directly observed family communication. [14-16] This confirms Dr. Wysocki's capacity to coordinate a multi-site intervention trial and the studies provided substantial experience with family problem solving and communication training interventions in T1DM. Many of the intervention educational materials and handouts developed for this work will be used in the planned trial.

4.5. Intensive Therapy for IDDM in Youths: Outcome Prediction (1-RO1-DK-50860-05). Dr. Wysocki was PI of this NIH-funded randomized, controlled trial of Intensive Therapy versus Usual Care that enrolled 147 children and adolescents with T1DM. The objective of this 5-year, 2-center project was to identify psychosocial predictors of treatment outcomes. Data collection was completed for 129 of the 147 families. Average HbA_{1C} was 8.2% for both groups at baseline and after 9 months of treatment was 8.3% for Usual Care and 7.7% for Intensive Therapy. [49] Incidence of severe hypoglycemia was 56/100 patient-years for Intensive Therapy and 45/100 patient-years for Usual Care, for a relative risk of 1.24. This study demonstrated the PI's capacity to conduct and disseminate a multi-center trial with this population, and to coordinate a complex clinical intervention and investigative protocol requiring close collaboration with medical colleagues.

The trial results showed greater absolute and relative glycemic benefit from Intensive Therapy for patients who were lower in self-management competence [50] and parental supportive involvement [51] at enrollment than those with more favorable status. Thus, youths who might be considered poor candidates for intensive therapy enjoyed more glycemic benefit from it. These findings suggest that adolescents with suboptimal diabetic control might also derive benefits from adding CGS to T1DM care. The pertinence of this intensive therapy trial for the present application is that patients with initially poor glycemic control, self-management competence and parental support ultimately realized greater benefit from intensive therapy. The findings underscore the present emphasis on evaluating the impact of CGS use by adolescents with sub-optimal glycemic control.

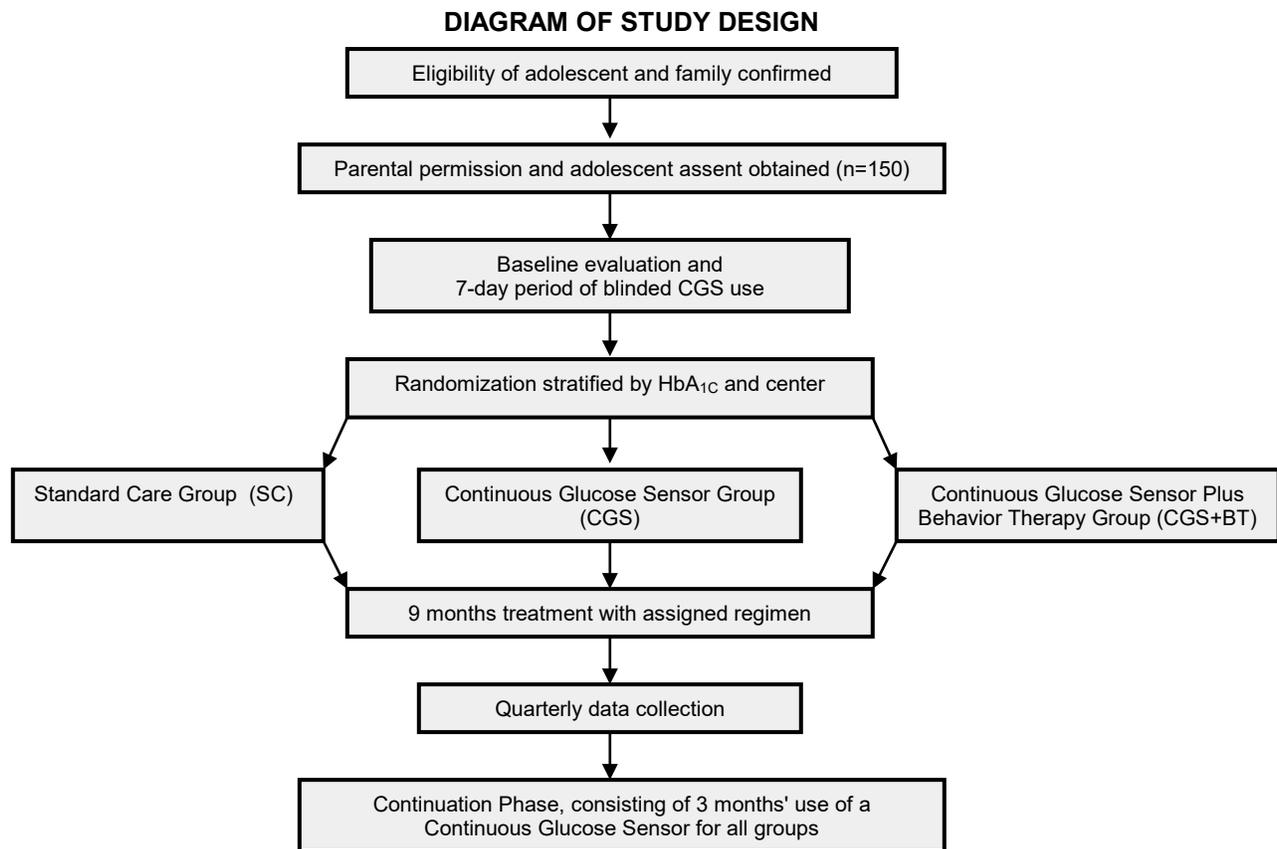**4.6. Publications on Self-Monitoring of Blood Glucose.** Dr. Wysocki has published on the therapeutic impact of SMBG and CGS. [45, 57, 101, 140-142] He was an invited speaker at the ADA 1994 Consensus Conference on Self Monitoring of Blood Glucose. His interest in optimizing the benefits of CGS is a logical extension of these interests. Relevant publications are listed in Section 7. These papers emphasize Dr. Wysocki's lasting

interests in the psychological context of evolving glucose monitoring technology. These papers also argue that such variables will affect therapeutic outcomes as these technologies are disseminated into clinical practice.

4.7. Summary. Dr. Wysocki has many qualifications for conducting the planned study, including previous CGS research, directing and contributing to multi-center clinical trials with this population, studies of psychological aspects of T1DM management and evaluation of behavioral interventions to enhance family management of T1DM. The proposed study is a logical extension and integration of this prior work that would evaluate a specialized behavioral intervention targeted to optimize therapeutic benefits of CGS technology.

5. RESEARCH DESIGN AND METHODS

5.1 Experimental Design. We propose a randomized controlled trial in which 150 adolescents with T1DM and their primary diabetes caregivers will be randomized to 9 months in one of three experimental conditions.

DIAGRAM OF STUDY DESIGN

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┌─────────────────────────────────────────────┐
│  Eligibility of adolescent and family confirmed │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ Parental permission and adolescent assent obtained (n=150) │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│            Baseline evaluation and            │
│         7-day period of blinded CGS use        │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│  Randomization stratified by HbA₁c and center │
└─────────────────────────────────────────────┘
```

| Standard Care Group (SC) | Continuous Glucose Sensor Group (CGS) | Continuous Glucose Sensor Plus Behavior Therapy Group (CGS+BT) |

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┌─────────────────────────────────────────────┐
│       9 months treatment with assigned regimen │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│             Quarterly data collection          │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ Continuation Phase, consisting of 3 months' use of a │
│     Continuous Glucose Sensor for all groups   │
└─────────────────────────────────────────────┘
```

- **Standard Care (SC)**: Intensified T1DM therapy based on conventional finger-stick SMBG and either insulin pump or multiple daily injection regimens and the use of carbohydrate counting and insulin dose correction factors. The incorporation of a CGS device into diabetes management presumes the intent to strive for optimal glycemic control. Hence, patients on conventional, fixed dose insulin regimens would not represent an appropriate comparison group for the two groups described below.
- **Continuous Glucose Sensor (CGS):** The SC regimen above augmented by use of a CGS for glucose monitoring, managed by a physician, diabetes educator and dietitian as in typical clinical practice. Parents and youths will receive very detailed training in all aspects of CGS use and interpretation.
- **Continuous Glucose Sensor Plus Behavior Therapy (CGS+BT):** The CGS regimen above supplemented with a psychological intervention targeting family diabetes management behaviors that are hypothesized to mediate benefit from CGS use.

After the 9-month Randomized Phase, all three groups will be offered a 3-month Continuation Phase during which youths would receive the CGS regimen as above. The goal of all three regimens will be to achieve HbA₁c $\leq$ 7.0% while minimizing risks for severe hypoglycemia. A 9-month duration for the Randomized Phase was selected because: 1.) DirecNet data suggests that frequency of CGS use declines among youths and this continues beyond 6 months; 2.) Prolonged CGS use may change T1DM self-care behaviors and we hope to observe this over a sufficient interval. 3.) We hope to achieve adequate statistical power for evaluation of

effects on severe hypoglycemia; 4.) Multiple data collection points for the primary outcomes capitalize on the strengths of individual growth modeling; 5.) A longer duration would delay availability of these important data. The 3-month duration for the Continuation Phase of the study was chosen because it is sufficient time for those randomized to the SC group to benefit from CGS use and it was a sufficient incentive in past DirecNet studies to achieve recruitment and retention goals and to be fair to study volunteers. The Continuation Phase will provide an incentive for SC participants to enroll and remain active in the study during the 9-month randomization phase. In the DirecNet and JDRF studies, access to CGS use was a key reason many families chose to enroll. It will also enable evaluation of the maintenance of intervention effects among CGS+BT youths. Deterioration of CGS+BT gains during the Continuation Phase would provide further evidence of the intervention's effectiveness. It will also permit evaluation of the longer-term CGS use by the CGS group, by tracking the degree to which those youths maintain CGS use over 12 months. Finally, it will enable replication of CGS benefits among SC youths who elect to use CGS during the Continuation Phase.

5.2. Participants. A sample of 150 youths with T1DM will be recruited from Nemours Children's Clinics (~50/center) in Wilmington, Delaware and in Orlando and Pensacola, Florida. Participants will not be recruited in Jacksonville because ongoing studies there would impede recruitment for this study. Nemours registrations show 914 current T1DM patients at the three sites who will be in the targeted age range (11 to <17 years old) at the start of enrollment. Of these, 518 patients (57%) have $HbA_{1C} \geq 7.5\%$, and this will probably increase as these patients age. The combined clinical populations at the three sites have been growing by about 300 T1DM patients annually, and so there should be over 550 eligible patients by the start date. The proposed sample size is justified in Section 5.13. With 35-45% recruitment rates in prior similar studies, and the likelihood that 15-20% of prospective youths are likely to be excluded based on the enrollment criteria, achievement of the recruitment goal requires that the study draw upon three clinics. Based on similar studies, we expect <10% attrition over the 12-months, yielding complete data on at least 135 youths. The parent or other caregiver who is most involved in each child's diabetes care will be required to participate, and other caregivers will be allowed to participate. Eligibility criteria were designed to enroll appropriate candidates for use of a CGS device who have recently achieved suboptimal HbA_{1C}. These criteria include:

- Age of child $\geq$ 11 years and < 17 years. This age range was chosen because families of adolescents often struggle with diabetes management. Youths $\geq$ 18 years old may be likely to leave home during the study.
- Duration of diabetes $\geq$ 2 years or $\geq$ 1 year with negligible stimulated c-peptide level, to exclude those with significant residual pancreatic insulin production.
- *Most recent $HbA_{1C} \geq 7.5\%$ and $\leq 10.0\%$ or mean HbA_{1C} over the prior 12 months within that same range.*
- *Youth has never used a CGS device for clinical management of diabetes.*
- Absence of any other medical conditions that, in the opinion of the attending endocrinologist, would impede completion of the study protocol.
- Youths may not be on daily glucocorticoid medications due to hyperglycemic effects of these agents.
- Intention to remain in the same region and to maintain diabetes care at the enrolling center for 12 months.
- Not enrolled in special education for mental retardation, autism or severe behavior disorders.
- Primary diabetes caregiver not diagnosed or in treatment for major depression, psychosis, bipolar disorder or substance use disorder within the 6 months prior to enrollment; Child not in an inpatient psychiatric unit or day treatment program during the 6 months prior to enrollment.
- Family has working telephone service.

The objective is to enroll 150 youths with T1DM with HbA_{1C} above target despite treatment with intensified T1DM regimens. *We limited enrollment to youths with $HbA_{1C} \geq 7.5\%$ and $\leq 10.0\%$ since they have much to gain in terms of improved glycemic control, reduction of health care costs and deferral of complications. Youths with $HbA_{1C} < 7.5\%$ have different goals for adding CGS to diabetes care, such as decreased severe hypoglycemia and glycemic variability rather than reduction in HbA_{1C}., while those with $HbA_{1C} > 10.0\%$ may be unable to use CGS safely.* Inclusion of two sub-samples with differing primary outcomes would create analytic problems that are avoided with a more homogeneous sample. The JDRF Artificial Pancreas Project will enroll a sub-sample of patients with $HbA_{1C} < 7.0\%$, while our study will make a unique contribution by focusing on adolescents with suboptimal glycemic control.

5.3. Stratified randomization *Youths entering the study must have been on a T1DM regimen for ≥ 6 months comprising either a "basal-bolus" multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII; insulin pump) regimens using carbohydrate counting and insulin correction factors. To promote equality of the groups in HbA_{1C}, randomization will be stratified by two HbA_{1C} levels: $\leq 8.8\%$ and $>8.8\%$. Separate*

randomization lists will be used for each center and HbA_{1C} stratum. After the baseline evaluation, adolescents within each stratum will be randomized with equal probability to the three groups (SC, CGS or CGS+BT) so that each center randomizes similar numbers into each group and so that the groups are similar in HbA_{1C}.

5.4. Representation of Genders, Minorities and Children. We will ensure a diverse sample via taxi fare, meal vouchers, and payment for child care to enable low-SES families to enroll. We will provide 15 personal computers for families who do not have one for CGS and SMBG downloads. Test strips for SMBG will be provided to those lacking insurance coverage. Written materials will be translated into Spanish and back-translated into English. Sampling goals will be: <u>Gender</u>: 50% boys, 50% girls; <u>Children</u>: All enrolled patients are <18; <u>Race</u>: 80% Caucasian; 20% African-American; <u>Ethnicity</u>: 90% Non-Hispanic; 10% Hispanic.

5.5. Measures. We will measure biomedical, behavioral and psychological outcomes and potential mediators or moderators of those outcomes. Questionnaires will be scored automatically with an optical scanner.

<u>**Measures Collected at Baseline Only**</u>

<u>**General Information Form (GIF)**</u> This form used in our prior studies records the child's age, sex, date of birth, date of diagnosis of diabetes, treatment regimen, family composition, parents' marital status, and each parent's occupation and highest level of educational attainment. We will calculate the Hollingshead Four Factor Index of Social Status, an index of socioeconomic status (SES). [144]

<u>***Diabetes Problem Solving Interview (DPSI)***</u> *This is a structured interview validated in the FMOD trial that assesses parents' and youths' skills in the correction and prevention of unwanted blood glucose fluctuations. [75] Respondents are given 2 of 12 available diabetes scenarios and asked these questions about each: 1.) What is the diabetes problem here? 2.) Why is this a problem? 3.) What would happen if he/she did nothing? 4.) Tell me all the ways this problem could be fixed; 5.) How would you fix this problem? 6.) How would that solution work? and 7.) How would you know if you really fixed the problem? Responses are audio-recorded and then coded with scenario-specific scoring rules. An in-press paper verified the psychometric properties of the instrument and showed that baseline DPSI scores predicted youths' HbA_{1C} over 9 months. [75]*

<u>**Measures Collected Quarterly**</u> The following measures will be obtained at each quarterly diabetes clinic visit:

<u>**One-Week "Blinded" CGS Use**</u> As in the JDRF Artificial Pancreas Project, prior to randomization, each family will be given a "blinded" CGS device (glucose feedback disabled) to use for 7 days and to return to the clinic for downloading. A minimum prerequisite for randomization will be at least 96 hours of analyzable CGS data. In addition to providing valuable data, this will serve as a "run-in" period to screen out participants who cannot comply with basic requirements and enable them to withdraw if they find CGS use to be intolerable (6 of 451 JDRF participants did so). Blinded CGS use will recur at 3, 6 and 9 months. CGS data obtained from SC participants in this manner will be compared to comparable data obtained during CGS use by those in the CGS and CGS+BT groups. Periodic 7-day samples of CGS data will be randomly selected from these participants' downloaded CGS data from within the month prior to each quarterly clinic visit.

<u>**Hemoglobin A_{1C} and other medical variables**</u> Finger-stick blood samples will be obtained for central laboratory HbA_{1C} assays at Baseline and each 3 months. For eligibility verification and clinical use, HbA_{1C} will be measured on DCA-2000 analyzers (Bayer Diagnostics Inc.) at each site as usual. [146] Blood samples will be obtained at each quarterly visit and sent to the Baptist Medical Center lab in Jacksonville using the sample collection and shipping protocol that is currently used in the FMOD trial. Assays will be run on a Tosoh Analyzer using cation-exchange HPLC to separate hemoglobin fractions, including stable A_{1C}, by a buffer gradient of increasing ionic strength. Coefficients of variation range from 2-3%. Several studies have shown high correlations between HbA_{1C} measured by DCA-2000 versus central labs using such HPLC, but there is consistent bias in DCA-2000 results so that central lab measurement is needed. [132] Other medical variables that will be obtained quarterly include Tanner Stage (breasts for females; genitalia for males; pubic hair for both), height, weight, Body Mass Index, linear growth velocity, and details of T1DM regimens.

<u>**Glucose meter with memory**</u> All patients with T1DM at these clinics use glucose meters with memory, enabling storage of SMBG results by date and time. Downloading stored data provides a complete record of the patient's SMBG results. Patients will bring their meters to all clinic visits for downloading and discussion of treatment changes. Adolescents will receive a $10 gift card at each clinic visit if they bring their blood glucose meters with them for downloading, a procedure that has yielded 94% adherence in the FMOD trial.

Downloaded data will yield descriptive statistics and measures of glycemic variability described below. The project will provide SMBG test strips to those without insurance coverage for them.

Continuous Glucose Sensor Diabetes Nurses will be trained by representatives of each CGS company, and with an on-line curriculum that will soon be on the JDRF website. [149] Kim Englert, R.N, a Diabetes Nurse in the JDRF Artificial Pancreas Project, will coordinate bi-weekly video-conferences for study nurses before enrollment and monthly case discussions in the first 2 years. Patients in the CGS and CGS+BT groups will select, with the help of diabetes nurses and physicians, the available CGS device that best matches their preferences for use during the study. The devices and supplies will be provided without charge. The same will apply to SC participants during the 3-month Continuation Phase. For the CGS and CGS+BT groups, a 7-day continuous sample of CGS data will be selected randomly from the months prior to the 3-month, 6-month and 9-month study visits to provide profiles for direct comparison to blinded CGS data for the SC group. Adolescents will be paid $10 for downloading the CGS device and sending the data to the coordinating center monthly. In the DirecNet and JDRF studies, virtually all families have been able to arrange this using either their own computers or one owned by a relative, neighbor or employer. The study will provide a home computer, internet access and training for up to 15 low-SES families.

Glycemic Variability Kovatchev's Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) are derived from SMBG values [104-108] and they reflect cumulative deviations of low and high glucose values from the logarithmic midpoint of the normal range. The LBGI and HBGI were validated as predictors of severe hypoglycemia and HbA_{1C}, respectively. The LBGI integrates the weighted values of each BG value that is below 112.5 mg/dl, the logarithmic midpoint of the normal range. The LBGI can be calculated over any interval ranging from a single SMBG result to multiple tests. The HBGI is calculated similarly from BG readings above 112.5 mg/dl. Kovatchev et al. have developed another metric derived from SMBG data, the Average Daily Risk Range (ADRR) and compared prediction of hypoglycemic and hyperglycemic events based on the ADRR with predictions from other indices of variability. [109] The ADRR was the best predictor of both hypoglycemic and hyperglycemic events. The proposed study will permit validation of the ADRR with children, which has not been done. Kovatchev et al. have also validated methods of quantifying glycemic variability for CGS data (Poincare Plots; blood glucose rate of change; Markov Chain interpretations) and these methods also warrant study in children. [110-113] We will calculate all of these measures of glycemic variability quarterly from SMBG data (all groups) or CGS data (patients using CGS). For patients randomized to SC, we will calculate these indices based on the 7-day periods of blinded use of a CGS device at Baseline, 3-months, 6-months and 9-months. Comparisons of these measures as predictors of severe hypoglycemia will enable a direct comparison of the utility of SMBG and CGS for predicting those events. Kovatchev and colleagues have also shown that these indices are sensitive to changes in diabetes regimens such as initiation of pramlinitide [111] and islet cell transplantation. [112] Kovatchev and Clarke [112-113] have recently reported that the initial effect seen after adding CGS to T1DM therapy is reduced glycemic variability followed by decreased HbA_{1C}. The proposed study will examine whether similar effects occur in our sample during CGS use. Dr. Kovatchev's consultation provides added assurance that the substantial CGS data to be collected in this study will yield important contributions in the analysis of blood glucose dynamics and the validation of measures of glycemic variability.

Hypoglycemia Diary As in our intensive therapy trial and DirecNet studies, parents will record youths' hypoglycemic episodes detailing the child's symptoms, date and time of the episode, results of SMBG tests, possible contributing factors, and the type of treatment. Hypoglycemia will be categorized by the Diabetes Nurse as Moderately Severe (requiring assistance from another person), or Severe (including seizures or loss of consciousness). Parents will report these events by phone, fax or e-mail to the clinic promptly after the episode. The nurse will interview the parent and patient to verify that the reported episode meets the criteria for severe hypoglycemia, to attempt to specify the cause of the event and to educate the family in an effort to prevent recurrence. The low frequency of severe or moderately severe hypoglycemia may impede treatment of these variables as primary outcomes in the statistical analyses. If so, we will analyze Kovatchev's measures of glycemic variability that are empirically validated indices of risk for severe hypoglycemia that confer the added analytic advantage of being continuous measures rather than discrete events. [102-113]

Diabetes Self Management Profile This 24-item structured interview yields subscale scores for five domains of diabetes adherence (Exercise, Diet, Hypoglycemia, Glucose Testing and Insulin) and a total adherence score. [83,147] Cronbach's alpha coefficient was .76 for the total score and inter-rater agreement was .94. The correlation between total scores of parents and adolescents was .72. Correlations with HbA_{1C} reported by

several research groups were consistently significant (range -.25 to -.60). [14, 51, 147] Youths and parents will be interviewed separately by telephone by trained staff at Nemours-Jacksonville who are not associated with the diabetes clinical teams. Some interviewers will be native Spanish speakers. Interviews will be audio-recorded for later scoring and reliability checks. We will also record the frequency of SMBG testing and the extent of CGS use from computer downloads as additional indices of treatment adherence.

Glucose Monitoring System Rating Questionnaire This instrument was developed for the JDRF Artificial Pancreas Project to permit direct comparison of conventional SMBG using a home glucose meter to conventional SMBG augmented by use of a CGS device. By contrast, the CGM Satisfaction Scale [56-57] was constructed by DirecNet to obtain participants' ratings of satisfaction with and impact of CGS devices that they had used for 3 months. The 25 items were drawn from the earlier 44-item CGM Satisfaction Scale and re-worded such that participants rate the glucose monitoring system they are using (SMBG with or without CGS). Preliminary data from the JDRF trial show that the revised instrument has equally sound psychometric properties as the CGM Satisfaction scale, with the added advantage of enabling direct comparisons of SMBG and CGS within and between patients. Alpha coefficients were .93 for parents and .89 for youths. Parent-Youth agreement was r = .61. Test-retest reliability was .71 for parents and .59 for youths at 3 months.

Blood Glucose Monitoring Communication Questionnaire This is an 8-item scale on which respondents describe their communication and affect about SMBG data. [79] It is a three-choice Likert scale, with higher scores indicating more frequent negative affect around SMBG. Internal consistency was .77 for 153 youths and .82 for parents, parent and adolescent scores correlated significantly, and 1-year test-retest reliability was .70. Scores correlated significantly with HbA_{1C}, diabetes-related conflict and quality of life. This measure will enable assessment of the extent to which provision of CGS data impacts emotional reactions to glucose levels and evaluation of the moderation of CGS treatment benefits as a function of scores on this measure.

Hypoglycemia Fear Survey This scale [84-85] measures worry and behavior related to hypoglycemia. Separate parent and youth versions have been validated. [84-85] This measure will clarify if CGS use affects anxiety related to hypoglycemia. *Since the content of this measure emphasizes aversion to experienced hypoglycemia rather than apprehension about its occurrence, we have added four items to evaluate this latter construct.*

Diabetes Family Responsibility Questionnaire Anderson et al [93] validated this measure of the degree to which 17 diabetes-related tasks is a parent, child or shared responsibility. This scale has been used in multiple T1DM studies [11-16, 21-23] and its psychometric properties have been strong consistently. This measure will enable assessment of the degree of parental involvement in diabetes management as a moderator/mediator of benefit from CGS use and whether CGS use, in turn, yields changes in this aspect of family function.

Parental Support Interview Wiebe's [95-96] semi-structured interview assesses youths ratings of parents' emotionally supportive involvement in T1DM care. Children who reported low levels of parental support had worse treatment adherence and higher HbA_{1C}. [95] The measure focuses on emotionally supportive involvement of parents, rather than instrumental involvement as in the Diabetes Family Responsibility Questionnaire. [93]

Diabetes Responsibility and Conflict Scale This scale [97] assesses parent-child conflict over 15 diabetes tasks. A recently validated revised scale has made it more applicable to modern T1DM regimens. [148] We have used this scale in several studies and have found excellent internal consistency (alpha .86 to .92). Only the conflict items will be used, and these should be sensitive to effects of CGS use on parent-child conflict.

PedsQL Diabetes Module This is a 28-item questionnaire with separate forms for parents and youths. [136] The DirecNet Navigator studies showed positive effects of CGS use on this index among adolescents but not parents. Participants in those studies were highly compliant and enthusiastic patients with very favorable quality of life at baseline. Quality of life improvement due to CGS use could be more readily detectable in the proposed study since less favorable baseline scores are expected due to the enrollment criteria.

Readiness to Change Questionnaire This brief scale, utilized previously by Sobell and colleagues [137-139] in other brief intervention studies, yields a convenient measure of motivation for change. It will be obtained quarterly from CGS+BT participants with regard to their selected target behaviors.

5.6. Cost-Effectiveness During 4 selected 2-week periods during months 18 through 36, all clinicians will record the time spent in clinical interactions with participants. These "time-sampled" recordings will include all activities related to clinical diabetes care, including clinic appointments, telephone contacts, e-mail exchanges, downloading of glucose meter or CGS devices, interpretation of downloaded data, etc. Activities that are done

for research purposes only (recruiting, informed consent, questionnaire administration, data transmission) will be excluded. Clinicians will record the duration, nature and purpose of each clinical contact (clinic, phone, e-mail) or other clinical activity (downloading, CGS or meter maintenance, provision of supplies) with each patient using methods employed successfully in Dr. Wysocki's intensive therapy trial. The ratio of time dedicated to Intensive Therapy patients to that for Standard Care patients during that study was about 4.5:1 for Diabetes Nurses, 3:1 for Dietitians and Psychologists and 1.3:1 for Physicians. The similarity of these estimates to those reported in the DCCT supports this method as a valid estimate of the degree of health professional time devoted to patients receiving varied interventions, permitting a reasonable derivation of the per-patient incremental costs for the CGS and CGS+BT regimens relative to the SC regimen. *We anticipate that the personnel time for the CGS groups will decline as the study proceeds, but distributing the observation periods throughout the study will yield a valid estimate of the relative personnel requirements for each condition. From these "time-sampled" cost estimates we will extrapolate the per-patient personnel costs of each of three conditions for the entire 9-month Randomized Phase. At quarterly clinic visits, parents will report the occurrence of hospitalizations, emergency room visits, and clinic visits. These reports will be verified by the Diabetes Nurse by medical records checks whenever possible. The costs for hospitalizations, ER visits and clinic visits will be obtained from the involved medical facilities. The retail costs of CGS devices and supplies will be included. Cost effectiveness of the CGS and CGS+BT will be evaluated descriptively both by direct comparison of the estimated costs of SC, CGS and CGS+BT and by reporting the cost per 0.5% improvement in HbA$_{1C}$ during the study for each group. These descriptive analyses will also focus on whether the added costs associated with the CGS regimens are offset by reductions in health care utilization (clinic visits, emergency room visits, hospitalizations) for those groups relative to Standard Care.*

5.7. Measurement schedule. In the measurement schedule below, "P" indicates collection of the measure from parent, "A" = from adolescents and "B" = from both parents and youths. All measures will be translated into Spanish and back-translated into English by native Spanish speakers. Participants may choose whether to complete the English or Spanish versions. Internal consistency and test-retest reliability will be calculated for each measure based upon data collected in the proposed study.

MEASUREMENT SCHEDULE

Measure	Study Visits (Months)				
	0	3	6	9	12
General Information Form (P)	•				
Glucose Meter memory downloads (A)	•	•	•	•	•
CGS Device downloads (A)	•	•	•	•	•
Measures of glycemic variability (A)	•	•	•	•	•
Hypoglycemia Diary (B)	•	•	•	•	•
HbA$_{1C}$ (A)	•	•	•	•	•
7-Day Blinded CGS use (SC only)	•	•	•	•	•
Diabetes Self Management Profile (B)	•	•	•		•
Glucose Monitoring System Rating Scale (B)	•	•	•	•	•
BG Monitoring Communication Questionnaire	•	•	•	•	•
Hypoglycemia Fear Survey (B)	•	•	•	•	•
Diabetes Family Responsibility Questionnaire (B)	•	•	•	•	•
Wiebe Parental Involvement Interview (A)	•	•	•	•	•
Diabetes Responsibility & Conflict Scale (B)	•	•	•	•	•
PedsQL Diabetes Module (B)	•	•	•	•	•
Readiness to Change Questionnaire (B) (CGS+BT only)	•	•	•	•	•
Diabetes Problem Solving Interview (B)	•				

The only copyrighted instrument being administered is the PedsQL quality of life questionnaire, but Nemours owns a site license that permits free use and distribution for research purposes at all Nemours entities. Consequently, it will be possible to enable administration of the various measures via a secure internet connection using the Opinio software platform. This functionality will enable participants to complete questionnaires from anywhere that provides internet access at any time within the 2 week period immediately preceding each quarterly diabetes clinic visit. If participants are unable to accomplish this, the questionnaires will be available for hard-copy administration at clinic visits and they will be encouraged to do so during waiting times before and during their visits. This flexibility should enable participants to control the amount of time dedicated to study participation on clinic visit days.

5.8. Procedures. Prior to randomization, all participants will complete the 7-day period of blinded CGS use. Data from the blinded CGS use will not be used for clinical management for the SC group. Participants who complete this run-in period will then complete the Baseline evaluation. Randomization will be stratified on Baseline HbA$_{1c}$ ($\leq$8.8% and >8.8%) and center. After the Baseline evaluation, the Diabetes Nurse will call the Project Coordinator at NCC-JAX to report the adolescent's HbA$_{1C}$. A randomization list will dictate the

adolescent's group assignment. The nurse will inform the family of their group assignment and then schedule an appointment with them for CGS training and with an endocrinologist to initiate intensive therapy.

The **Standard Care** regimen will have these features:
- Targets consisting of pre-prandial blood glucose of 70-120 mg/dl, 90 minute postprandial blood glucose below 180 mg/dl and 3AM blood glucose >65 mg/dl, unless the attending endocrinologist determines that a particular patient's risk of severe hypoglycemia requires revised targets.
- Targeted $HbA_{1c} \leq 7.0\%$ unless the attending endocrinologist determines that a particular patient's risk of severe hypoglycemia requires revised targets.
- Targeted absence of severe hypoglycemic episodes and minimization of symptomatic hypoglycemia.
- Multiple daily subcutaneous insulin injections of a long acting (e.g. glargine) and short acting (e.g. Novalog or Humalog) insulin **or** continuous subcutaneous insulin infusion with an insulin pump. There will be enough patients using each type of insulin regimen to permit statistical comparisons between them.
- Completion of 4-6 blood glucose tests daily using a meter with memory function. Patients in all 3 groups will be instructed to use SMBG data to guide treatment decisions and insulin adjustments.
- Completion of a 3AM blood glucose test monthly using a meter (SC group only).
- Quarterly clinic visits with a Pediatric Endocrinologist.
- Monthly telephone consultation with a Diabetes Nurse.
- Advanced diabetes education regarding real-time and retrospective use of blood glucose data to minimize glycemic variability and optimize proportion of time spent in normoglycemia.
- Dietary management using carbohydrate counting with appropriate nutritional education and counseling.
- Referral for psychological services as needed based upon the opinion of the attending endocrinologist.
- Incorporation of therapy advances that emerge before or during the study. The SC group may not use a CGS device during the 9-month randomization phase except in the blinded 7-day CGS use periods.
- *A "rescue procedure" will be employed for any youth whose HbA_{1C} remains above 9% for 2 consecutive visits or whose HbA_{1C} increases by more than 1.0% over baseline or who has more than one episode of severe hypoglycemia. As would typify clinical practices with similar patients, this will consist of offering monthly clinic visits with a diabetes nurse, weekly telephone consultation with the nurse and referral to a dietitian, social worker, psychologist or psychiatrist at the discretion of the treating endocrinologist.*

Patients randomized to SC will be treated as above but they will not use a CGS during the 9-month Randomized Phase. Given the enrollment criteria for this study, a baseline mean HbA_{1C} for this group can be expected to be about 8.8% and we anticipate a 0.2% increase (~0.15 SD) to about 9.0% during the 9-month randomization phase of the study.

All study participants will receive the above SC regimen. CGS and CGS+BT regimens will differ as below.

Continuous Glucose Sensor (CGS) With consultation from the diabetes team, patients randomized to CGS will select a CGS device for use during the study from among those that can be made available for use in this study. Appropriate training and counseling will be provided by the diabetes nurse to include:
- Parents and youths will be carefully trained in the safe and proper use of the selected CGS device and associated analytic software. *Substantial emphasis will be placed on making treatment decisions suggested by CGS results only after a confirmatory SMBG check is done. CGS use will be portrayed as a supplement to SMBG, not a replacement. [149] Training will cover real-time and retrospective analysis of CGS data and appropriate responses to alarms, using a book by H. Peter Chase, M.D. [150] and the JDRF website "Continuous Glucose Monitoring Classroom" that will soon be available for public access.*
- Weekly phone contact initiated by the diabetes nurse during the first month of CGS use.
- 24-hour telephone access to an on-call pediatric endocrinologist.
- Week-day telephone access to the diabetes nurse to report device-related problems.
- A 2-week follow-up visit with the diabetes nurse to download the CGS device and further education about responding to CGS data prospectively and retrospectively. Clinical insulin dose adjustment algorithms previously developed and validated in DirecNet studies will be taught to adolescents and parents. A JDRF website will soon be available that will offer additional teaching materials and supports designed for patients using CGS as a component of diabetes management.
- A 1-month follow-up visit with the diabetes nurse to review the family's use of the insulin adjustment algorithms and to evaluate the need for individual refinement of the algorithms.

- The diabetes nurse will be permitted to bring selected adolescents and parents in for interim clinic visits as needed for remedial education to ensure that the adolescent and parent have the requisite knowledge and skills required for deriving optimal benefit from use of the CGS.

Based on the DirecNet Navigator pilot study, we expect HbA$_{1c}$ to decline by approximately 0.3 SD over 9 months to a mean value of about 8.4% for this group.

Continuous Glucose Sensor Plus Behavior Therapy (CGS+BT) Patients randomized to CGS+BT will receive the same education and care as the CGS group. Also, a mental health professional (MHP; e.g. a licensed counselor, post-doctoral fellow, licensed clinical social worker, or psychologist) will deliver a behavioral intervention within a motivational interviewing context that is designed to identify each family's unique behavioral, cognitive or affective barriers and resources pertaining to optimal CGS use, negotiate with the youth and parent a plan addressing the identified targets, and assist the family in implementing, evaluating and possibly refining the selected intervention over the ensuing months. The MHP's role in this study will be very similar to that of the Health Advisor interventionists in the FMOD trial and we will make extensive use of a manual, intervention handouts, telephone contact protocols, intervention plan outlines and other such materials that were developed in that study. *A preliminary draft of the intervention manual appears in the Appendix, to be further refined prior to initiation of the study. Each MHP will receive extensive training in Motivational Interviewing coordinated by our expert consultant, Linda C. Sobell, Ph.D.* The MHP will guide the family in preparing an action plan that will include responsibilities of each family member in implementing it, methods of measuring the plan's effectiveness, and a timeframe for evaluation and refinement of the plan. At a minimum, the MHP will telephone the teen and parent 2 weeks before and 2 weeks after diabetes clinic visits to review the family's success with their plan, and trouble-shoot with them any problems they report in implementation of the plan. Like the diabetes educators, the MHP's will be permitted to make appointments with CGS+BT families for more phone contacts and supplemental face-to-face clinic visits as needed to provide the assistance they need to benefit from CGS. MHP's will see each CGS+BT family at every diabetes clinic visit, including with the Diabetes Nurse or Dietitian as needed. MHP's may target for intervention any problem that a family may report that may be impeding the adolescent from using the CGS optimally. *MHP's will document the date, time, duration and content of all telephone and face-to-face encounters with CGS+BT families.* MHP's will be trained to identify certain negative behaviors related to CGS use that could be intervention targets and to recognize instances in which families could benefit from targeting the promotion of positive behaviors rather than on remediation. Below are some CGS-specific target behaviors that MHP's may select with CGS+BT families. Additional target behaviors are likely to be identified during the study.

The overall intent of this intervention trial is to maximize the therapeutic benefits obtained through augmentation of T1DM management with the use of CGS technology. This will be achieved through the application of best clinical practice of behavior therapy with adolescents when applied to the specific behavioral processes that modulate their benefits from CGS use. Components of this intervention, as described in greater detail in the appendix, were selected based on these key criteria:
- *Reliance on motivational interviewing techniques to encourage patients and parents to play a central role in the specification of behavioral goals, target behaviors and intervention methods.*
- *Emphasis on parent-adolescent interaction around CGS use as an intervention target.*
- *Extensive empirical support for all intervention components, ideally obtained from pediatric T1DM studies.*
- *Flexibility to enable application to unique CGS-related behavioral problems.*
- *Extent to which M.A.-trained therapists can learn to implement the intervention component proficiently.*
- *Ease of dissemination of intervention materials and methods to other clinical sites.*

The structure of the planned intervention rests on three components, the first two of which will be delivered in the same manner to all participants and the last of which will be tailored to each family's unique targeted behaviors and contextual circumstances:

1.) Reliance on Motivational Interviewing techniques to establish the patient-centered and family-centered focus of the intervention, and to assist participants in identifying and prioritizing goals that will be targeted by the behavior therapy intervention components. Motivational Interviewing is viewed here not as an intervention in and of itself, but rather as an entre' to enhance engagement with other intervention components.
2.) All participants will receive training in Problem Solving and Communication Skills using materials and methods developed and validated in Dr. Wysocki's trials of Behavioral Family Systems Therapy for Diabetes. In addition, evidence of common Cognitive Distortions pertinent to family management of T1DM will be

monitored and treated as communication errors using the above model, as has been done in our prior BFST trials. This approach includes extensive reliance on the common behavior therapy practices of instructions, feedback, modeling, rehearsal and individualized behavioral homework assignments.
3.) Mental Health Professionals (MHP's) who will deliver the intervention will use a systematic method for the selection and implementation of behavior therapeutic intervention components to achieve improvements in the identified target behavior(s). For each of the anticipated target behaviors, the MHP will strive to select the intervention approach that has the strongest empirical support as the "first choice" approach to utilize with the family. This determination will be guided by a thorough compendium of empirical studies supporting various behavioral interventions in pediatric T1DM that appears in the appended intervention manual. Consistent with the Motivational Interviewing framework, parents and youths will play a central role in selecting from among recommended intervention components and tailoring the details to their preferences and circumstances. Failure of the selected strategy to achieve the therapeutic goal can result in the MHP modifying the intervention approach after proposing and defending the alternative approach to the satisfaction of Dr. Wysocki. A similar approach will be employed in selecting intervention strategies for families who identify intervention goals or target behaviors other than those that have been anticipated based on prior experience.

Target Behaviors: Expected targets of intervention will include these "negative" behaviors: Inadequate frequency of CGS use; Resistance to completing calibration SMBG checks; "Ignoring" of alarms warning of impending hypo or hyper-glycemia; Resistance to doing finger-stick SMBG when CGS readings seem inaccurate; Adolescent concern about parental "snooping"; Inordinate family attention devoted to BG levels; Arguments about BG levels; etc. Targets of intervention will also include efforts to promote "positive" behaviors such as: Problem solving to prevent unwanted BG fluctuations; Parent-youth teamwork and brainstorming around CGS results; Goal setting for improved BG control; Conducting "experiments" to measure effects of dietary intake, exercise, etc. on subsequent BG levels and changes; Improving family communication about out of range BG levels; Parent-youth negotiation about diabetes management goals, responsibilities, etc. Other target behaviors are likely to be identified as the study proceeds.

Intervention Intensity: Given the planned five sessions, the planned intervention is conceived as a brief, relatively low intensity intervention with quite specific treatment foci. Although each of the primary constructs of the Behavioral Family Systems model will be measured, [117, 145] we do not expect to observe profound treatment effects on complex, deeply ingrained systemic anomalies that may characterize some families. Instead, these theoretical constructs will be evaluated as moderators of CGS+BT treatment effects.

Qualifications and skills of the Mental Health Professionals (MHP): MHP's will have prior experience in the delivery of brief behavioral interventions, ideally from among existing staff or associates of the respective diabetes clinics. Those who do not have substantial clinical experience with T1DM will receive extensive training, including directed readings, observation of diabetes education with newly diagnosed families, accompanying physicians or nurse practitioners in clinic visits with T1DM patients, and training in the use of all glucose meters, insulin pumps and CGS devices that might be used by study participants. MHP's will utilize behavioral intervention tactics that have been empirically validated with this population. MHP's will not be involved in recruitment of participants or with collection of study data to minimize possible reactivity and bias.

In addition to relying on empirically validated behavior therapy techniques, the intervention for each patient/family will rely heavily upon motivational interviewing techniques. These methods have been validated with adolescent substance abuse, truancy, obesity and dietary habits [132-135] and have shown promise with adolescents with T1DM. [23-25] *All MHP's will receive training in Motivational Interviewing [28-30, 132-135] as an adjunct to adolescent behavior therapy in two 2-day workshops conducted by Linda C. Sobell, Ph.D., a pre-eminent behavior therapist who has extensive experience integrating these two approaches. A draft of the workshop curriculum and plan is included in the appended intervention manual.* After negotiated selection of target behaviors and intervention goals, the MHP will guide each parent-adolescent dyad/triad in the selection and design of an appropriate behavior therapy intervention that may draw upon one or more validated approaches. Problem solving training and family communication training materials and methods used in the BFST studies will be employed. [11-16] Behavior modification and behavioral contracting methods [121-125] have been validated in studies targeting increased frequency of SMBG in adolescents and these techniques are readily adaptable to similar behaviors in the CGS context. Self-monitoring and goal-setting [151-152] are commonly used behavior therapy methods that are effective in promoting behavior change. Behavioral homework assignments are a staple of behavior therapy interventions. Pertinent materials from the FMOD study and BFST studies will be utilized in the proposed study, for example, to explore glycemic effects of dietary behaviors or to measure the

frequency of targeted parent-adolescent communication problems. Cognitive behavior therapy [153-154] and cognitive restructuring methods validated in the BFST studies [11-16] will be applicable to situations in which either parents or adolescents exhibit cognitions that are impediments to initiating or maintaining behavior change or in which anxiety is a key element of the target problem. Drawing upon treatment manuals developed and used in the BFST and FMOD studies, a CGS-specific intervention manual has been developed for this study. The further refinement of this manual will facilitate cross-site consistency in the intervention and enhance dissemination of the methods to other clinical settings once the research has been completed.

Intervention visits will be scheduled to coincide with other study visits. The MHP will see each CGS+BT family at the Baseline visit, the 2-week and 1-month follow-up nursing visits and each quarterly clinic visit during the 9-month Randomized Phase of the study, for a total of 5 scheduled clinical encounters. Telephone follow-ups will be scheduled at 2-weeks before and 2-weeks after each clinic visit, with more frequent contacts or e-mail communication if deemed necessary by the MHP. MHP's will be allowed to see CGS+BT families for separate face-to-face appointments if needed. The Baseline, 2-week and 1-month visits will be dedicated to delivery of a common psychoeducational curriculum to each CGS+BT family and to initial assessment of each family's current adaptation to T1DM and its management. The content of this curriculum will include basic principles of behavior change, positive reinforcement, problem solving skills, healthy communication, and conflict resolution. Examples of specific behavior change goals related to optimal CGS use will be employed to illustrate each of these principles in that context. The conclusion of the 1-month visit will be dedicated to assisting each family in identifying one or more targeted behaviors related to CGS use, ideally focusing on both positive and negative behavior change goals. CGS+BT visits beginning with the 3-month visit will be dedicated to evaluating and refining the behavior change plan(s) developed at prior visits.

All face-to-face contacts between MHP's and CGS+BT families will be audio-recorded and sent to Dr. Wysocki for evaluation and coding for treatment integrity, using previously developed coding systems used in prior trials. This will include recording of the target behaviors and the type of behavior therapy methods used. Deviations from the intervention manual will result in re-training of the MHP involved as well as possible revision of the intervention manual to clarify sources of ambiguity.

Based upon effect sizes achieved in our studies with similar samples, we anticipate that the CGS+BT group will achieve and maintain a mean HbA_{1C} of about 7.4% for effect sizes of 1.2 SD relative to the SC group and 0.8 SD relative to the CGS group. The sampling plan is designed to achieve adequate statistical power to detect effects of this magnitude. A 0.8 SD treatment effect is clinically significant. In terms of glucose variability and risk for hypoglycemia (measured by the LBGI), a recent study of 40 days CGS use (Navigator), 20 days blinded followed by 20 days un-blinded, showed that the LBGI was reduced by ~0.35 SD during the period of un-blinded use of CGS compared to the blinded use period. [109] We anticipate larger effects in our trial due to its longer duration and enrollment of a sample with more pronounced baseline glycemic variability.

5.9. Data Management and Statistical Analysis Plans. Prior to excusing a parent or youth after completion of any type of data collection, the researcher will ensure that missing items are completed and that errors are corrected. Measures will be recorded on scannable forms for scoring using the Opscan 4.0 optical scanner (NCS-Pearson, Inc., Minneapolis, MN). Data will be double-entered and cross-checked before final computer entry. Data files will be backed up nightly, password-protected and stored on a local area network. Participants will be assigned study ID numbers that will be used rather than names to label completed questionnaires, paper records, etc. All raw data obtained during the project will be stored in locked file cabinets without names recorded on these items. The researchers will maintain a list of ID numbers paired with participants' names and will keep this list in a password-protected computer file separately from other data. Signed informed consent forms, which will contain participants' names, will also be stored separately in locked cabinets. Error checking routines will be created as part of the database application. Weekly reports will be generated for the purpose of monitoring the accrual patterns and for the completeness of data.

Statistical analysis will begin with treatment of missing data, preliminary descriptive analysis and visual inspection of distributions. [155-156] Appropriate transformations of variables will be used to restore normality if needed. Baseline values of the primary outcome and predictor variables will be compared to determine if there are significant pretreatment differences between the groups that require adjustments. Visual examination of scatter plots, histograms and other graphical summaries will be used to identify possible associations or treatment effects of interest. Where multiple statistical comparisons are planned, we will make appropriate multiplicity adjustments. [155-158] Internal consistency will be calculated for each psychometric measure based on

data from this study and only those with alpha $\geq$ .70 will enter data analyses. Upon completion of these preparatory activities, we will apply Individual Growth Modeling [160-161] to test the hypotheses listed below (see Section 5.12 for details).

5.10. Hypotheses. The following hypotheses, corresponding to the three specific aims, will be tested:
Hypothesis 1: Adolescents in CGS+BT will show more improvement in glycemic control (HbA$_{1C}$, Kovatchev's measures of glycemic variability derived from SMBG and CGS data, and proportion of CGS values in the normal range) compared with those in SC and CGS over the 9-month Randomized Phase.

Hypothesis 2: Adolescents in CGS+BT will realize more improvement in diabetes-related behavioral outcomes (Diabetes Self-Management Profile; PedsQL Diabetes Module; Diabetes Responsibility and Conflict Scale; Hypoglycemia Fear Survey; Blood Glucose Monitoring Communication Questionnaire: Blood Glucose Monitoring System Rating Questionnaire) compared with those in SC and CGS and in scores on the CGM Satisfaction Scale (CGS vs CGS+BT only) over the 9-month randomization phase of the study.

Hypothesis 3a: Improvements in HbA$_{1C}$ during the 9-month Randomized Phase will be moderated by adolescents' and parents' baseline status on the following measures: Socioeconomic status; Family composition; Adolescent age; Diabetes Problem Solving Interview, Parent-Adolescent Relationship Questionnaire; Diabetes Family Responsibility Questionnaire; Wiebe Parental Supportive Involvement Interview; and Diabetes Responsibility and Conflict Scale).

Hypothesis 3b: Improvements in HbA$_{1C}$ during the 9-month Randomized Phase will be mediated by improved scores on the Diabetes Self-Management Profile, Diabetes Problem Solving Interview, Diabetes Responsibility and Conflict Scale, Wiebe Parental Supportive Involvement Interview, and Blood Glucose Monitoring Communication Questionnaire.

5.11. Other planned analyses. The proposed study will yield a rich data set, permitting many interesting analytic directions. Of special interest will be analyses of 1.) Maintenance (CGS and CGS+BT) and replication (SC) of treatment effects during the 3-month Continuation Phase; 2.) Determination of the frequency of CGS use that is associated with improvement in the various indices of glycemic control; 3.) Validation of mathematical models of CGS dynamics as predictors of the occurrence of severe hypoglycemia and HbA$_{1C}$; 4.) Evaluation of the temporal course of changes in glycemic variability and changes in HbA$_{1C}$ during CGS use; 5.) Descriptive analyses of cost effectiveness as described in section 5.6; 6.) Between-group comparison using survival analysis of the time to first occurrence of severe or moderately severe hypoglycemia; and 7.) Prediction of changes in frequency of CGS use over time based on demographic and behavioral variables.

5.12. Analytic procedures. *The randomized experimental design in this study will collect longitudinal data in a sequence of 5 time points at about 3-month intervals (Baseline, 3, 6, 9 and 12 months) from 3 treatment groups (SC, CGS, CGS+BT). Individual Growth Modeling [160-164] will be applied to evaluate the treatment effects specified in the above hypotheses. The IGM approach, which also has been termed multilevel modeling, hierarchical linear modeling, or mixed effects modeling, is a particularly powerful and flexible approach for evaluating treatment effects within longitudinal data sets. The IGM approach has numerous advantages over traditional methods including 1) It compares the change of the outcome variable, such as HbA$_{1C}$, over time instead of comparing mean differences at specific time points; 2) It does not require that time points be equally spaced or data be collected at the same time at each time point for all participants. In fact, participants may have individually varying data collection over time during the study; 3) The covariates, such as site differences in this study, can be easily included in the model to adjust for these possible nuisance effects. 4) The covariance structure of the repeated outcome measures can be modeled and statistically compared to obtain more accurate estimates; and 5). It handles missing values flexibly—all available measurements of the outcome variable can be included in the analysis, thus increasing the power of the study.*

The basic individual growth model consists of two levels. The level-1 model is the estimation of the shape of individual change curves over time. The level-1 model for linear change is:

$$Y_{it} = \pi_{0i} + \pi_{1i} * Time + \varepsilon_{it}$$

where Y_{it} is the outcome variable for subject i assessed at time t, π_{0i} is the expected intercept for subject i, π_{1i} is the expected change rate (the slope) in the outcome for subject i, and ε_{it} is the within random error for subject i conditional on that subject's change parameters. In this study, the outcome variables will be the

youth's glycemic control, Kovatchev measures of glycemic variability derived from SMBG and CGS data, Diabetes Self-Management Profile, Diabetes Responsibility, and Conflict Scale, etc., that will be repeatedly measured over time. The variable Time in the level-1 model will be measured in months, starting from the baseline of the study to the time of data collection.

The level-2 models are used to test whether time-invariant predictors are related to the initial status and the change of the outcome over time. The treatment effect in this study will be coded as a dummy variable, a time-invariant predictor of change to be evaluated in the level-2 models. Other examples of time-invariant predictors include socioeconomic status, parent marital status, and gender that are thought to be stable over time, and will be tested as the moderators of the treatment effect. Specifically, the level-2 models are

$$\pi_{0i} = \beta_{00} + \beta_{01} * X_i + \mu_{0i}$$
$$\pi_{1i} = \beta_{10} + \beta_{11} * X_i + \mu_{1i}$$

where β_{00} and β_{10} are the grand means for the intercepts and the slopes estimated in the level-1 model, respectively. β_{01} and β_{11} are regression coefficients for X_i which is a time-invariant variable for subject i, with μ_{0i} and μ_{1i} the random errors in the models. When X_i is the treatment effect coded as a dummy variable, a significant β_{01} indicates that the outcome variable is different for the treatment groups at the baseline. Our major research interest is to evaluate coefficient β_{11} ------ a significant β_{11} shows that the change in the outcome variable is different for treatment groups due to the intervention program.

Both the basic level-1 and level-2 models in IGM can be extended by including more variables in the models. In general, variables measured repeatedly over time, also referred to as time-varying or within-subject variables, are included in level-1 models. The between-subject variables, also referred to as time-invariant variables and usually only measured at baseline, are included in level-2 models. The shape of the curves for the outcome variables will be determined first. Time-invariant and time-varying predictors will then be examined for their relationship with the outcome using the estimated growth factors of the trajectories. The 3 primary hypotheses proposed in this study will be evaluated within the IGM framework. SAS Proc Mixed and Proc Glimmix will be used for the IGM analysis for the 3 primary hypotheses.

Hypothesis 1: Adolescents in CGS+BT will show more improvement in glycemic control (HbA$_{1C}$; Kovatchev's measures of glycemic variability derived from SMBG and CGS data; Proportion of CGS values in the normal range) compared with those in SC and CGS over the 9-month Randomized Phase.

To evaluate the treatment effects on the change of glycemic control over time, HbA$_{1C}$ measured from baseline to end of study will be the outcome variable in the level-1 model. A participant without missing values will have a total of 5 measures of HbA$_{1C}$. The time interval between baseline and the measure of each HbA$_{1C}$ in the unit of months will be the Time variable in the level-1 model. The shape of the HbA$_{1C}$ trajectory will be determined statistically by comparing a linear model and a quadratic model using the AIC and BIC indices produced by SAS Proc Mixed. In level-2 models, X_i will be a dummy variable indicating treatment groups. For example, to evaluate the treatment effects between CGS+BT and CGS groups, the dummy variable will be coded 1 for CGS+BT and 0 for CGS. A significant coefficient of the dummy variable will indicate that the change rate of HbA$_{1C}$ over time is different for the two groups due to the treatment effect. A similar strategy will be applied to evaluate the difference in the change of HbA$_{1C}$ between CGS+BT and SC, and CGS and SC groups. Since Kovatchev's measures of glycemic variability and the proportion of CGS values in the normal range are on continuous scales that are comparable across repeated measures, these variables are also appropriate to use as outcome variables with IGM estimated using SAS Proc Mixed.

If the treatment groups are significantly different in the outcome measures, it is of interest to examine whether the difference in treatment groups persists after adjusting the covariates that are known to be associated with the outcome. This process will be conducted by including covariates in the IGM framework. For example, demographic variables (SES, parent marital status, etc.) and disease variables (diabetes onset age, duration, etc.) can be included in the models as covariates to improve the precision of estimation when evaluating the treatment effect. If the dummy variable is still significant with the covariates in the model, the interpretation is that the treatment accounts for some unique variance in the change of the outcome over time above and beyond the effects of the covariates. The effect of site difference will be included as a between-subject covariate with a random effect. Specific programming to include the site difference as a random effect using SAS Proc Mixed will follow Dmitrienko et al for clinical trial data collected from multiple sites. [162]

The IGM approach allows for comparison and selection of the appropriate covariance structure of the outcome measured over time. Candidate structures include compound symmetry (CS), autoregressive order-1 AR(1), unstructured, and AR(1) with random effect which will be specified in SAS Proc Mixed. The AIC and BIC indices will be used for model selection, with smaller AIC or BIC values indicating relatively better models fitting the data. The selection of an appropriate covariance structure may further reduce the bias of model estimation.

Hypothesis 2: Youths in CGS+BT will realize more improvement in diabetes-related behavioral outcomes (Diabetes Self-Management Profile; PedsQL Diabetes Module; Diabetes Responsibility and Conflict Scale; Hypoglycemia Fear Survey; Blood Glucose Monitoring Communication Questionnaire: Blood Glucose Monitoring System Rating Questionnaire) compared with those in SC and CGS over the 9-month randomization phase of the study.

The data analysis strategy to evaluate Hypothesis 2 will be similar to that applied to Hypothesis 1 within the IGM framework. Specifically, in the level-1 model the outcome variables will be the Diabetes Self-Management Profile, the PedsQL Diabetes Module, the Diabetes Responsibility and Conflict Scale, the Hypoglycemia Fear Survey, the Blood Glucose Monitoring Communication Questionnaire, and the Blood Glucose Monitoring System Rating Questionnaire. The Time variable in the level-1 model will be the time interval from baseline to the time of measurement in month. In level-2 models, a dummy variable indicating treatment groups will indicate the treatment effect. A significant coefficient of the dummy variable will show that the change rate of the outcome is different for the treatment groups due to the treatment program.

To adjust for the effects of important covariates in examining the treatment effect, the covariates will be included in level-1 and level-2 models. The time-varying covariates will be included in the level-1 model and the time-invariant covariates will be in level-2 models. There are two advantages of adjusting the covariates when evaluating the treatment effect. First, the adjusted analysis will improve the power of evaluating the treatment effect because of increased precision of estimation. [163-165] By adjusting a covariate in a linear model, the precision gained is proportional to the correlation between the covariate and the outcome variable. Second, omitting important covariates in the model may lead to bias of the results. Therefore, important covariates will be included in the models to evaluate the group difference in all the outcomes. Similar to the strategies in Primary Hypotheses 1, the effect of site difference will be treated as an additional between-subject variable as a random effect in the models.

Hypothesis 3a: Improvements in HbA$_{1c}$ during the 9-month Randomized Phase will be moderated by adolescents' baseline status on the following measures: Socioeconomic status; Family composition; Adolescent age; Parent-Adolescent Relationship Questionnaire; Diabetes Family Responsibility Questionnaire; Wiebe Parental Supportive Involvement Interview; and Diabetes Responsibility and Conflict Scale).

Analysis of moderator effects can identify variables that are predictive of intervention outcomes. . For example, in Hypothesis 3a, if the treatment effect on HbA$_{1c}$ differs as a function of the family's socioeconomic status, then socioeconomic status is a moderator variable. It is important to evaluate the heterogeneity of the treatment effect to identify the subgroups that derive lesser or greater benefit from the intervention.

The testing of moderators will be conducted within the IGM framework outlined above. Specifically, HbA$_{1c}$ will be the outcome and Time will be measured in months in the level-1 model. A dummy variable indicating treatment groups will be the predictor in level-2 models. A product term of the proposed moderator and the dummy variable, together with the main effect of the moderator candidate, will be entered into the level-2 models. A significant coefficient of the product term indicates that the candidate is a significant moderator. The analysis process will be carried out using Socioeconomic Status, Family composition, adolescent age at baseline, and scores on the Diabetes Problem Solving Interview, Parent-Adolescent Relationship Questionnaire, Diabetes Family Responsibility Questionnaire, Wiebe Parental Supportive Involvement Interview, and Diabetes Responsibility and Conflict Scale separately to determine significant moderators.

To interpret the effects of any significant moderators, estimated individual growth factors (e.g., the slope in linear trajectory) will be compared among subgroups of the moderator. The analysis will reveal subgroup differences in the change of outcome due to the treatment effects. For moderators measured on continuous scales, such as adolescent age at baseline, appropriate categorization will be applied for meaningful interpretation of the findings. Important covariates will be included in the models to adjust the possible effects

of the covariates. Within this model, site differences will be treated as a between-subject covariate to adjust for its possible effects on the outcome.

Hypothesis 3b: Improvements in HbA_{1C} during the 9-month Randomized Phase will be mediated by improved scores on the Diabetes Self-Management Profile, Diabetes Responsibility and Conflict Scale, Wiebe Parental Supportive Involvement Interview, Diabetes Problem Solving Interview, and Blood Glucose Monitoring Communication Questionnaire.

Mediators are process variables that are affected by the treatment effect and are believed to have effects on the outcome. Mediator analysis will help us to understand the mechanisms why the treatment is effective. In mediator analysis we will determine whether the treatment effect is wholly or partial due to the mediators. Following Baron and Kenny, [166] traditional mediator analysis using cross-sectional data involves three regression equations, the outcome regressed on the treatment effect, the outcome regressed on both the treatment and the mediator, and the mediator regressed on the treatment. In the multi-level modeling framework, Krull & MacKinnon [163] introduced a detailed process of mediator analysis that has advantages over the methods used in the context of cross-sectional data. We will closely follow the approach recommended by Krull & MacKinnon [163] to examine the possible mediators proposed in Hypothesis 3b.

Specifically, in the IGM framework described above, HbA_{1C} will be the outcome in level-1 models and the treatment effect will be a dummy variable indicating treatment groups in level-2 models. Since all mediating variables in this study (the Diabetes Self-Management Profile, Diabetes Responsibility and Conflict Scale, Wiebe Parental Supportive Involvement Interview, and Blood Glucose Monitoring Communication Questionnaire) are within-subject variables measured repeatedly during the study, these mediators will be included in the level-1 model. Following Krull & MacKinnon, [163] the mediator analysis involves three stages of IGM: HbA_{1C} predicted by treatment alone, HbA_{1C} predicted by both treatment and the mediator, and the mediator predicted by the treatment alone. Combining the results from the three stages of IGM, we can determine if a candidate is a whole, partial, or non-mediator of the treatment effect in improving HbA_{1C}.

5.13. Sample size and statistical power. *Power analysis and sample size estimation were based on projected treatment effects on HbA_{1C}, the primary outcome measure, as shown in the figure below To estimate sample sizes needed in the three groups for sufficient statistical power, a Monte Carlo simulation study was conducted using MPlus (Version 5). [164] The Monte Carlo procedure is the most common and the preferred methodology to estimate sample size in Individual Growth Modeling. [167-168] In a Monte Carlo study, random samples are generated repeatedly using the known population parameters with a specified sample size. The percentage of simulated samples that have reached significance on the parameters is the estimated power of the study. Thus, the required sample size can be determined accurately by varying sample sizes in a series of simulations. MPlus provides extensive facilities for conducting Monte Carlo studies on IGM. Our simulation study followed the procedures recommended by Muthen & Muthen, [164, 168] including generating missing values to reflect expected attrition and the pattern of missing data in the proposed study. The primary contrast of interest in this study is change in HbA_{1C} relative to baseline values among adolescents in the SC,*

Projected Effects on HbA_{1C}
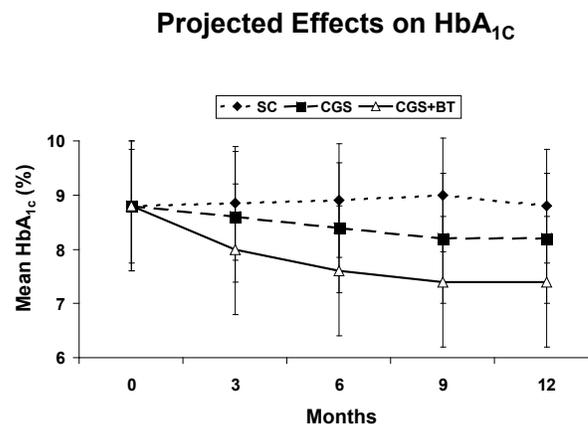
CGS, and CGS+BT groups. Based on the mean HbA_{1C} obtained in several prior trials at Nemours Children's Clinic in Jacksonville and the stated enrollment criteria, we expect that the baseline mean and standard

deviation values will be approximately 8.8% ± 1.2%. The standard deviation of HbA$_{1C}$ will increase gradually with each measure spaced about 3 months. At the end of 12 months, we expect a 0.8% difference in HbA$_{1C}$ between the CGS and CGS+BT groups. Assuming a standard deviation of approximately 1.5% at the end of the study, the effect size will be 0.533, a moderate effect size as defined by Cohen [169] that is clearly clinically significant. Based on the retention rates in our NIH-funded randomized trials, we anticipate an attrition rate <10% during the 1-year study. Therefore, enrollment of 150 patients (50 per group) should result in at least 135 (45 per group) at the end of the 9-month randomization phase of the study. We anticipate that about 120 participants (40 per group) will complete the 3-month Continuation Phase of the study.

Based on these parameters with 5 equally spaced measures of HbA$_{1C}$ (Baseline, 3, 6, 9, and 12 months) and random missing values, the Monte Carlo study with 3000 simulated samples showed that the power of the design is 94.5%. Muthen and Muthen [164, 168] also recommend that the parameter bias should not exceed 10% and standard error bias should not exceed 5%. All of these criteria were satisfied in the Monte Carlo study. A similar Monte Carlo study was conducted for estimating the statistical power contrasting the SC and CGS groups. We expect a mean difference of approximately 0.6% in HbA$_{1C}$ between the two groups at the end of the study. The Monte Carlo study showed with 50 participants in each group and approximately 10% missing values, the statistical power remains above 80%. Fan [167] compared the statistical power between IGM and the traditional Repeated Measures ANOVA with longitudinal data under different situations. Fan's conclusion was that IGM consistently showed higher power than Repeated Measures ANOVA to compare group differences in change over time. Since we will apply IGM to the evaluation of all three primary hypotheses, we are confident that the planned sample size offers sufficient statistical power in this study.

5.14. Data and Safety Monitoring. An external panel not otherwise involved in this study will serve on a Data and Safety Committee (DSC). The DSC membership will include a Pediatric Endocrinologist, a Certified Diabetes Educator and a Pediatric Psychologist who are not Nemours employees. The DSC will receive quarterly reports of recruitment statistics, gender and minority distributions of the samples enrolled at each center, frequency of SMBG and CGS use, summaries of minor adverse events, and a detailed description of any serious or unexpected adverse events on a standardized reporting form. Serious Adverse Events are those that result in death, a life threatening situation, hospitalization, disfigurement, disability or a congenital anomaly/birth defect, whether or not that event appears to be attributable to the study procedures. Unexpected adverse events will be events that were not described in the study protocol or informed consent documents. Events of either type will be reported as soon as possible after they occur to the PI, the DSC and the IRB. Special attention will be given to episodes of severe hypoglycemia, since this occurs more frequently among intensively treated patients. Treatment regimens will be "de-intensified" and glycemic targets raised for any patient experiencing an episode of severe hypoglycemia. Additional special attention will be given to the patients randomized to Standard Care to minimize the chance that any of these patients would endure significant deterioration in glycemic control. Adolescents with increases in HbA$_{1C}$ of more than 1.0%, who have HbA$_{1C}$ > 9.0% for two consecutive clinic visits, or who experience more than one episode of severe hypoglycemia during the study will be seen more frequently in clinic, or referred for additional diabetes education, nutritional counseling, or psychological/psychiatric services at the discretion of the treating endocrinologist, consistent with routines for patients not participating in this study at each clinic.

5.15. Project Time Frame. In the DirecNet and JDRF studies, preparation for trials such as that proposed here was very time-consuming and complex. The nursing and educational time required for training adolescents and parents to use and download the CGS device proficiently and to follow them clinically thereafter was also extremely labor-intensive. We have planned the time frame and personnel needs of the project accordingly to enable a realistic and careful evaluation of the treatment regimens being compared.

<div align="center">Months</div>

	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Form steering committee & DSC	■																			
Refine protocol	■	■	■																	
Negotiate CGS purchase	■	■																		
Write procedure manual	■	■	■	■																
Refine intervention manual	■	■	■	■																
Hire and train staff		■	■	■																
Consultant activities	■	■	■																	

Activity														
IRB and DSC reviews		■	■	■			■			■		■		■
Procurement & purchasing		■	■	■		■		■		■		■		■	■
Submit progress reports			■				■			■			■		■
Recruit participants		■	■	■	■	■	■	■	■	■					
Data collection and entry		■	■	■	■	■	■	■	■	■	■	■	■	■	■
Data cleaning & verification		■	■	■	■	■	■	■	■	■	■	■	■	■	■
Statistical analyses									■		■	■	■	■	■
Write journal articles											■	■	■	■	■
Submit renewal application													■		

The first 12 months will consist of preparatory activities including hiring and training project staff, training study nurses for certification on the CGS devices, insulin pumps and glucose meters to be used during the study, obtaining IRB approval, establishing procedures for data collection, transmission and storage, developing the study procedure manual, curriculum for CGS education and refining the intervention manual for use with the CGS+BT group. Recruitment of participants will begin at about month 12 and will continue until about month 36. Each of the three clinics will be expected to enroll approximately 2-3 patients per month, until the full sample of 150 adolescents has been enrolled at the combined sites. Based on experience with similar trials (JDRF, DirecNet and our Intensive Therapy trial), this pace of recruitment enables efficient completion of the research plan without rapidly overloading the clinical staff with patient encounters, phone contacts and follow-up visits as can easily happen with more rapid recruitment. As has been the case in similar trials, we expect the recruitment rate to taper off gradually. The clinical and educational demands associated with starting patients on CGS devices may exceed that associated with initiation of insulin pump therapy. While there are enough eligible patients, more rapid recruitment could overload the clinical staff and result in sub-optimal delivery of CGS-related education and management supports and compromise the internal validity of the study. The proposed recruitment rate ensures that each clinic will have no more than 30 active study patients concurrently, or about 20 patients in the two CGS groups. We judge the extra demands entailed in CGS-based regimens to be manageable by a 50% FTE Diabetes Nurse and a 10% FTE physician. Data collection will continue through approximately Month 48-51. DSC conference calls will occur once prior to the initiation of recruitment of participants, and then at 6-month intervals beginning 6 months after recruitment commences. A competing renewal application will be prepared and submitted at approximately Month 51. Data cleaning and verification, statistical analysis and dissemination of project results will occur during the final 9-12 months.

5.16. Limitations of the study. The most important limitation derives from the fact that CGS technology is changing rapidly and it is being incorporated rapidly into clinical care. We will utilize the most advanced CGS technology that is available to us when we begin recruitment. While the various manufacturers protect their research and development plans due to the highly competitive business environment, it is clear that each company has a new iteration of its device in development. Our prior interactions with the manufacturers in the DirecNet and JDRF work have cultivated a climate of collaborative trust with these companies. The proposed research could be seen by the companies as useful to them in seeking FDA approval for pediatric indications for their devices and for expanding the marketability of CGS to adolescents with suboptimal glycemic control. Thus, there is a strong likelihood that the proposed study can utilize the most advanced CGS technology at the time enrollment would begin. Regardless of the specific CGS devices used, the study will still yield valuable information about enhancement of the capacity to derive glycemic benefits from this technology through the provision of a targeted behavior therapy intervention. The study could also inform other studies of the prediction and facilitation of benefit from technological advances in other medical contexts. Also, we will permit study participants to change to CGS devices that may emerge during the study, consistent with our intention of evaluating variables affecting the achievement of glycemic benefits from CGS use in a generic sense rather than a focus on evaluating or comparing specific CGS devices.

Another conceivable limitation is that the study design was driven in part by the desire to keep the direct costs for the project below $500K in each year. This strategy was recommended by the NIDDK Program Officer responsible for behavioral science research. Completing the study in less than 5 years is not possible without exceeding that limit substantially or without major design changes.

6. INCLUSION ENROLLMENT REPORT

This report is not applicable since this is a new application.

7. PRELIMINARY STUDIES AND PROGRESS REPORT PUBLICATION LIST

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*:   Member of Writing Committee
**: Chair of Writing Committee

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8. PROTECTION OF HUMAN SUBJECTS

The Nemours Foundation has registered its three IRB's with the NIH Office of Human Research Protections and has an approved Federal-Wide Assurance (#00000293). The proposed studies and the associated procedures for parental permission (informed consent), adolescent assent and protection of research volunteers will be reviewed by the Nemours-Florida IRB. As chairperson of that IRB, Dr. Wysocki will recuse himself from the IRB's review of this study. Policies and Procedures for the Nemours Office of Human Subjects Protection are available at this URL: http://www.nemours.org/internet?url=no/nohsp/policies.html. The Nemours Foundation has recently applied for accreditation of its human subjects protection program by the Accreditation Agency for Human Research Protection Programs. Procedures for the protection of study participants in the proposed investigation are summarized below.

8.1. Description of participants and eligibility criteria: A sample of 150 adolescents with T1DM and at least one parent of each will be recruited from the three participating clinics (~50 per center). For each child, the parent or other legal caregiver who is most involved in the child's daily diabetes management will be required to participate, while the other parent will be encouraged, but not required, to participate. Eligibility criteria were designed to target for enrollment patients who might be considered clinically appropriate candidates for intensive therapy and for use of a CGS device. These criteria include:

- Age of child $\geq$ 11 years and < 17 years. This age range was chosen to maximize the yield of clinically useful information from this study regarding the appropriate selection of candidates for use of CGS devices. *Most recent HbA$_{1C}$ $\geq$ 7.5% and $\leq$ 10.0% or mean HbA$_{1C}$ $\geq$ 7.5% and $\leq$ 10.0% over the past three measurements prior to enrollment.*
- Duration of diabetes $\geq$ 2 years <u>or</u> $\geq$ 1 year with a negligible stimulated c-peptide level.
- *Adolescent treated on an intensified T1DM regimen for at least 6 months prior to enrollment, consisting of either continuous subcutaneous insulin infusion or a multiple daily injection regimen using carbohydrate counting and insulin dose correction factors to calculate pre-meal insulin dosing.*
- *Youth cannot have used a CGS device for clinical diabetes management in the past.*
- Absence of other systemic chronic diseases except well-controlled asthma and Hashimoto's thyroiditis.
- Intention to remain in the same geographic area and to maintain diabetes treatment at the enrolling center for the duration of the study.
- Willingness to accept random assignment to the experimental conditions.
- Not in special education for mental retardation, autism or severe behavior disorders.
- Parent not diagnosed or in treatment for major depression, psychosis, bipolar disorder or substance use disorder within the 6 months prior to enrollment.
- Child not hospitalized in a psychiatric unit or enrolled in a psychiatric day treatment program during the 6 months prior to enrollment.

Each of the three clinics will seek to enroll families of 50 children meeting the above eligibility criteria. Procedures will be established to ensure enrollment of children and families representing low-income racial and ethnic minorities. To minimize these impediments, we will offer evening and weekend appointments for

data collection, taxi fare, meal vouchers, reimbursement for child care and other such inducements to enable participation of members of racial/ethnic minorities who may be of lower socioeconomic status. Before beginning recruitment of patients, the Steering Committee will compile a report of the racial/ethnic composition of potentially eligible patients at each clinic. Then, each clinic will be given a sampling objective to ensure that the enrolled sample for the entire study achieves the following targets: Gender: 50% male, 50% female adolescents with diabetes; Children: All enrolled patients will be children; Race/Ethnicity: 70% Caucasian; 20% African-American; 10% Hispanic.

8.2. Sources of research material: Adolescents (11-<17 years old) with T1DM mellitus and their parents will complete a variety of questionnaires and structured interviews related to their experiences with intensive therapy for diabetes with conventional self-monitoring of blood glucose or the same therapy regimen augmented by use of a CGS. Patients will download data stored in memory by their blood glucose meters and by the CGS approximately monthly using personal computers as well as at periodic clinic visits. Questionnaires and interviews were selected to capture information on the typical range of reactions to these various diabetes regimens and to identify possible predictors of outcomes of these differing approaches. Finally, audio recordings will be made of intervention visits with the Mental Health Professionals for families in the CGS+BT group for the purpose of evaluation of treatment integrity and for recording details of the intervention process experienced by each family.

8.3. Methods of recruitment: The Diabetes Nurse or Research Assistant at each participating Nemours site will review upcoming appointments for diabetes visits in the Division of Endocrinology and Metabolism to identify potential participants. A brief study summary, signed by the PI and the patient's attending endocrinologist, and a copy of the informed consent form will be mailed to the parents about 10-14 days prior to the scheduled clinic appointment. In the letter, the parents will be told to expect a call from the project staff to answer their questions about the study and it will also give the parents the name and telephone number of the Diabetes Nurse or Research Assistant if they would prefer to call for this information. The Diabetes Nurse will offer to meet with the family just before or after the clinic visit to confirm their eligibility and to discuss their possible participation in the study. Those who are eligible and agree to participate will sign the Parental Permission and/or Adolescent Assent forms as appropriate and then be scheduled for a Baseline evaluation.

8.4. Assessment of research-related risks: Risks of participation include those associated with using a CGS, those associated with management of diabetes mellitus with an intensive therapy approach, those associated with remaining in standard care for diabetes and those associated with threats to privacy and confidentiality. We believe that these represent minimal risks as defined by the DHHS Office of Human Research Protection and by the Policies and Procedures of the Nemours Office of Human Subjects Protection.

Risks associated with the various CGS's that will be evaluated consist primarily of irritation of the skin in the area on which the device is worn. This can manifest as an edematous rash that was rated as more than mild in about 10% of children who have worn these devices in previous DirecNet studies. This complication can be reduced or prevented by proper hygiene and skin care before and after wearing the device and by rotating the site on which it is worn from one period to the next.

A further risk associated with CGS's is the possibility that they will provide inaccurate data on prevailing glucose levels, potentially leading to inappropriate decisions with respect to insulin, eating or exercise. CGS education for adolescents and parents will instruct them to make no adjustments to insulin, food intake or exercise based on CGS data alone and to always confirm the CGS readings by performing a conventional SMBG test. Patient education on use of these devices will emphasize the necessity for healthy skepticism regarding the sensor data and the necessity of completing finger-stick blood glucose checks whenever the sensor readings do not appear congruent with recent trends or with treatment events such as insulin administration, eating or physical activity. These potential risks have not materialized in the European GuardControl Trial or in any of the DirecNet or JDRF studies of CGS devices that Dr. Wysocki has participated in. Most patients and parents have quickly learned that CGS results must be confirmed by conventional SMBG before treatment actions are taken.

Finally, adolescents who are non-compliant with their diabetes regimens may also be noncompliant with responsibilities and precautions associated with CGS use. Adolescents who do not calibrate the CGS properly, who ignore alarms, or who do not complete confirmatory SMBG checks when necessary may face risks of

worsened glycemic control, rather than improvement, during CGS use. The planned education, monitoring of anticipated variants of noncompliance with CGS use, limited provision of replaceable sensors and rescue procedures all provide protections against these sources of risk.

Intensive therapy for T1DM provides extensive professional resources and involvement to provide the medical, educational, nutritional or psychological services and/or support that are necessary to achieve the closest approximation to maintenance of normoglycemia that can be achieved without unacceptable or clinically dangerous risks of severe hypoglycemia or unwanted weight gain. Since the DCCT, intensified therapy for youths with T1DM mellitus has become increasingly common, such that the mean HbA$_{1C}$ for patients entering our intensive therapy trial (8.2%) did not differ appreciably from the mean HbA$_{1C}$ levels reported for intensively treated adolescents in the DCCT. The achievement of near-normoglycemia in the DCCT was accompanied by a threefold increase in the occurrence of severe hypoglycemia among adolescent participants, as well as by unwanted weight gain. While these are legitimate risks as revealed by the DCCT, our experiences in our intensive therapy trial and recent continuous glucose sensor studies with children showed that both the absolute levels of these risks and the levels of these risks relative to patients treated with what has since become standard care for T1DM are both lower than those reported previously for DCCT adolescents. In the DCCT, intensively treated adolescents had about 86 episodes of severe hypoglycemia per 100 patient-years, compared with conventionally treated adolescents who had about 29 episodes per year, for a Relative Risk of 2.9. In our intensive therapy trial, patients in the Intensive Therapy (IT) group experienced 56 episodes of severe hypoglycemia per 100 patients per year compared with 45 episodes per 100 patient-years for the Usual Care (UC) group, for a Relative Risk of 1.24. Within the narrow range of HbA$_{1C}$ in which we were operating (means of ~7.7 for IT and 8.3% for UC), the correlation between HbA$_{1C}$ and frequency of severe hypoglycemia was -0.07 (ns) and the mean HbA$_{1C}$ levels of patients who had one or more episodes of severe hypoglycemia did not differ significantly from those who had no episodes. In fact, SH frequency in the IT group declined steadily during the study, to approximately 35 episodes per 100 patients per year during the last 6 months of the trial and this has been similar to the frequency of severe hypoglycemia observed in the various DirecNet CGS trials and pilot studies. Thus, treatment with intensive therapy yields only a modest increase in the risk of severe hypoglycemia compared with the current standard care for type 1 diabetes at Nemours Children's Clinics. A recent, larger study of intensive therapy in pediatric T1DM also showed that the anticipated risks of intensive therapy in this age group simply did not materialize in that study either. If, as expected, patients in the CGS and CGS+BT groups in this study realize a lower risk of severe hypoglycemia compared with patients in the SC group, then the former two groups of patients may experience a lower risk than do comparable patients receiving routine care for T1DM at these clinics.

Weight gain was also less of a problem for our IT patients compared with the DCCT adolescents. Mean BMI increased slightly for both groups, with a slightly higher mean BMI for the UC group throughout. The percentage of patients with BMI $\geq$ 25, a commonly used clinical cutoff for overweight, increased slightly during the study for both groups. BMI $\geq$ 30, suggestive of obesity, was evident in about 4-6% of enrolled patients at each data point. Changes in BMI and HbA$_{1C}$ were not correlated significantly in our study. Thus, unwanted weight gain was a minimal problem in our intensive therapy trial, although we will monitor its occurrence .

The SC group participants may not achieve substantial improvements in glycemic control during the initial 9-month Randomized Phase of the study since they will not be allowed to use CGS devices as part of their T1DM care. Nonetheless, these adolescents will be managed with intensive therapy regimens and they will be offered clinical and educational resources to permit improved glycemic control. Many adolescents achieve HbA$_{1C}$ $\leq$ 7.0% with such a regimen without using a CGS device. All SC patients will be offered 3 months' use of a CGS device during the Continuation Phase of the study.

Although the measures do not include norm-referenced scales to detect possible psychopathology, it is likely that some study participants will experience the onset or exacerbation of serious psychological or behavioral problems during the study. When any such instance is detected, the adolescent and family will be referred for evaluation and treatment through established referral sources in the various clinic communities. The draft intervention manual in the appendix includes explicit criteria for such referrals.

Completion of questionnaires, interviews and other data collection for the study carries risks associated with threats to privacy and confidentiality. All paper study forms and questionnaires will be labeled with a unique study ID code number rather than participant's names or other identifiers before being sent to the coordinating

center at Nemours-Jacksonville. Should any of these materials be lost, it will not be possible for others to identify the participant. Digital audio recordings of CGS+BT intervention visits will contain the participants' voices and are therefore potentially identifiable. All of the measures planned for collection in the proposed study have been used in the principal investigator's prior research without significant concerns being expressed by any participants. None of these measures seek participants' responses about potentially stigmatizing, embarrassing or illegal behaviors, thoughts or attitudes.

8.5. Assessment of research-related benefits: All patients who enroll in the study will receive intensive therapy for T1DM and may therefore achieve better glycemic control. Our Intensive Therapy patients achieved mean HbA_{1C} levels of 7.6%-7.7% that emerged after 3 months of treatment and remained near that level. Patients who are randomized to either CGS or CGS+BT may achieve lower HbA_{1C} levels than those in the SC condition and/or they may experience fewer episodes of severe hypoglycemia. SC participants will be allowed to use a CGS device during the 3-month continuation phase of the study. Assuming that all CGS's used in the study will have FDA approval for such therapeutic indications by the end of the study, all participants in the study will be allowed to keep their CGS's after the study. In order to continue using the device after the study, participants would then assume responsibility for the costs of purchasing additional sensors.

8.6. Safeguards to protect against risks: The most important risks faced by patients in the proposed study are possible deterioration in glycemic control and possible increased occurrence of severe hypoglycemia.

With respect to the risks of possible deterioration in glycemic control, patients in all three groups will be seen approximately quarterly by pediatric endocrinologists as well as by other members of the diabetes team as needed. Immediate telephone access to a pediatric endocrinologist on call will be available on a 24-hour basis. Diabetes educators, dietitians and other members of the diabetes teams are available by telephone during weekday business hours. All treatment regimens and targets will be in accord with the guidelines promulgated by the American Diabetes Association for this clinical population throughout the study. *A "rescue procedure" will be employed for any youth whose HbA_{1C} remains above 9% for 2 consecutive visits or whose HbA_{1C} increases by more than 1.0% over baseline or who has more than one episode of severe hypoglycemia. As would typify clinical practices with similar patients, this will consist of offering monthly clinic visits with a diabetes nurse, weekly telephone consultation with the nurse and referral to a dietitian, social worker, psychologist or psychiatrist at the discretion of the treating endocrinologist.*

The study design includes several protections against the risks of severe hypoglycemia:
- All patients will receive thorough, frequent assessments of severe hypoglycemia risks through repeated calculation of the Low Blood Glucose Index. These data are not routinely obtained for diabetes clinic patients and its availability permits counseling of patients and parents to reduce their individual risks.
- Targets for HbA_{1C} and daily blood glucose will be raised for any child who experiences an episode of severe hypoglycemia in an effort to reduce its recurrence. Also, following such events, the Diabetes Nurse will make a special effort to have the family keep the child's glucose levels on the high end of normal for the subsequent 2 weeks.
- Patients randomized to CGS and CGS+BT may have some protection against severe hypoglycemia if the clinical use of these devices achieves the expected outcomes.

8.7. Informed consent process: Parental permission (Informed consent) and adolescent assent will be obtained by the Diabetes Nurse. Parents will sign an IRB-approved parental permission and informed consent form. Adolescents will sign an IRB-approved adolescent assent form. All participating parents will receive a copy of the signed consent/assent forms for their records. The original signed consent/assent forms will be stored in a locked file cabinet accessible only by the Principal Investigator and project staff.

8.8. Protection of confidentiality: Confidentiality of information obtained from participants in this project will be protected to the full extent permitted by law. In accord with Nemours Policies and Procedures, all study staff will be required to show documentation of completion of required on-line curricula in human subjects protection and HIPAA research regulations. Each participant will be assigned a unique code number and the names and identities of participants associated with each code number will be known only to the research staff. All raw data and computerized data files will refer to participants only by code number and not by names, initials or other identifiers. No individually identifiable health information will be disclosed to any organization or individual that is external to Nemours. Digital audio recordings of CGS+BT intervention visits will contain images of participants' voices and will therefore be potentially identifiable. These recordings will be made

using digital voice recorders and will be stored in password-protected electronic files before transmission to the coordinating center. They will be labeled with participant ID numbers rather than names or other identifiers. Youths, parents and mental health professionals will be instructed to avoid using full names when referring to one another during these visits. The recordings will be deleted once they have been rated. All data will be stored in locked file cabinets and in password-protected computer files and no names will appear in any of these files. Signed parental permission and adolescent assent forms will be stored separately in locked file cabinets. Access to these files will be limited to the Principal Investigator and research staff as well as to those agencies and individuals who have legitimate legal rights and authority to inspect such records.

9. INCLUSION OF WOMEN AND MINORITIES

Each clinic will enroll families of about 50 eligible adolescents. The sampling plan ensures equitable representation of racial and ethnic minorities so that comparisons of minorities and non-Hispanic Caucasians are feasible. To encourage participation of minorities, we will offer evening and weekend appointments for data collection, taxi fare, meal vouchers, and reimbursement for child care to enable participation of members of minorities who are of lower socioeconomic status. Sampling objectives will ensure that the study achieves these targets: Gender: 50% male, 50% female adolescents; Children: All enrolled patients will be children; Race: 80% Caucasian; 20% African-American; Ethnicity: 90% Non-Hispanic and 10% Hispanic. The Florida and Delaware populations have become increasingly Hispanic over the past decade. The study questionnaires, informed consent and assent forms, and educational materials will be translated into Spanish by native Spanish-speaking persons and back-translated into English to ensure accurate translation. The three clinics will provide access to about 550 eligible patients, ensuring the enrollment of a diverse sample meeting these targets.

10. Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Clinical Use of Continuous Glucose Sensors in Adolescents with Inadequate Diabetic Control

Total Planned Enrollment: 150 parents (P) (90% of parents are expected to be female) and 150 youths (Y)

TARGETED/PLANNED ENROLLMENT: Number of Subjects (Adolescents)			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	8	7	15
Not Hispanic or Latino	67	68	135
Ethnic Category: Total of All Subjects *	75	75	150
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	15	15	30
White	60	60	120
Racial Categories: Total of All Subjects *	75	75	150

- The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."
-

11. INCLUSION OF CHILDREN

All enrolled patients will be children and adolescents between 11 and 17 years old at enrollment.

12. VERTEBRATE ANIMALS

Not applicable

13. SELECT AGENTS

Not applicable

14. MULTIPLE PI LEADERSHIP PLAN

Not applicable as there is one Principal Investigator

15. CONSORTIUM & CONTRACTUAL ARRANGEMENTS

Not applicable. All participating sites are operating entities of the Nemours Foundation and they share one Tax ID and DUNS number.

16. LETTERS OF SUPPORT

- Grafton Reeves, M.D.
- Mark Kummer, M.D.
- Jorge Daaboul, M.D.
- Boris Kovatchev, Ph.D.
- Rusan Chen, Ph.D.
- Linda C. Sobell, Ph.D.

17. RESOURCE SHARING PLAN

Data Sharing Plan

The proposed study will be registered on www.clinicaltrials.gov as soon as an award statement is received, ensuring that information about the study will be available to interested parties and so that they will understand when archived data will be made available. Publications resulting from this study will also be shared on the pertinent NIH website in accord with the NIH policies and procedures regarding internet sharing of publications resulting from NIH-supported investigations. The intervention manual will be made available to appropriately qualified psychologists, child and adolescent psychiatrists and other licensed mental health professionals with appropriate training and experience.

The proposed research will include data from 150 adolescents with type 1 diabetes and their parents recruited through 3 diabetes clinics. Data gathering will include audiotapes of telephone interviews; however, access to these tapes will not be permitted as it will be impossible to assure anonymity of participants. The final dataset will include: self-reported demographic and behavioral data from the participants obtained periodically during the study; laboratory data from quarterly clinic visits including, but not limited to, data on pubertal development, hemoglobin A1c, patterns of health care utilization, and psychological adjustment; self-report data collected at the quarterly clinic visits including information about health status and diabetes management; coded interactions from the audiotapes mentioned above. Identifying information will include, but not be limited to, age, age of diagnosis, gender, clinic identifier, height, weight, race/ethnicity, and socioeconomic status. Even though the final dataset will be stripped of identifiers prior to release for sharing, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

The dataset will be redacted to protect subjects' identities. This project has specified research questions that address both the long-term effects of the intervention and longitudinal changes in specific variables. Datasets will be made available through a data enclave immediately following acceptance for publication of papers addressing all research questions specified in the protocol only when those data are not to be used to address subsequent specified research questions. The data will be kept for at least 3 years after the publication of the last article based on the proposed research questions.

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