Study Protocol

Official Title: Family-Centered Tailoring of Pediatric Diabetes Self-Management Resources

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Project Summary:
The primary goal of this project is to compare the effectiveness of a family-centered approach to diabetes self-management resources (intervention) with the untailored approach of usual care. Diabetes self-management resources will be tailored to families' unique self-management barriers as identified by a 10-minute survey tool called PRISM (Problem Recognition in Illness Self-Management). Based upon the results of PRISM, families will receive self-management resources aligned to address their identified barriers. We will coordinate group-based delivery of the resources with routine diabetes clinic visits. These group-based resources will be delivered in four 75-minute sessions over a year. To assess the effectiveness of the intervention, we will examine glycemic control (A1c), fear of hypoglycemia, and quality of life for the child and parent.

Background and Significance:
Children with type 1 diabetes face complex self-management regimens, making adherence challenging and ultimately resulting in poor blood sugar control.[1, 2] Several common barriers interfere with diabetes control such as limited knowledge or challenges with staying motivated.[3] In addition, both children and parents experience reduced quality of life, compared to those not living with diabetes.[4] Efficacious strategies exist to improve diabetes self-management and quality of life, including but not limited to diabetes education or motivational interviewing.[5-11] Patients and families often do not access these strategies, citing inconvenience of attending and lack of belief that the resource will help their specific issues.[8, 12]

To ensure resources do address each family's specific issues, a family-centered approach has been suggested.[3, 13] Family-centered care engages the family in the decision-making about the child's health and well-being, specifically around the types of information and support that the family may need to achieve better health outcomes. In this study we will take a family-centered approach to providing diabetes self-management by identifying families' unique self-management barriers through the 10-minute survey tool called PRISM.

We conducted a pilot study (n=65) of our intervention, focusing on two PRISM barrier domains, 1) Family Teamwork and 2) Understanding and Organizing Care. At the pilot's conclusion, 75% families in ADA-based Diabetes Education and 67% in Family Teamwork had completed the year-long trial, similar to rates in published trials.[14, 15] Although not powered to detect statistical significance, the participants receiving the PRISM-tailored self-management resources demonstrated a highly clinically significant mean 0.8-point reduction in A1c at the conclusion of the pilot study.

Specific Aims:
The aims of this three-year study are to improve glycemic control and quality of life (QOL) for children with type 1 diabetes and their parents. We hypothesize that families receiving the intervention (family-centered tailoring of diabetes self-management resources) will have improved glycemic control for their children and improved QOL for the child and parent.

Research Design and Method
Study Population:
The total number of subjects is 300 families (family being a child with type 1 diabetes and their parent).

Inclusion:
1) Children ages 8 years to 16 years with type 1 diabetes and their parent/guardian; 2) Receive care at either the UW-Madison Pediatric Diabetes Clinic (UW) or the Pediatric Diabetes Care Program at Children's Hospital of Wisconsin (CHW); 3) Planning to continue care at their clinic site for the next 2 years; 4) Can speak and read English; 5) Diagnosed with type 1 diabetes for ≥ 12 months.

Exclusion:
1) Newly diagnosed with type 1 diabetes (< 12 months); 2) A subject in prior preliminary work for this study

Subject Identification and Recruitment:
Recruitment for this study will occur in three ways: 1) in-person recruitment by research team members at the UW or CHW diabetes specialty clinics; 2) email or regular mail recruitment sent to UW or CHW diabetes clinic patients; and 3) flyers/notices at the diabetes clinics or on their websites.

For in person recruitment, a member of the healthcare team will approach a potentially eligible child and parent/guardian at their visit to ask if interested in learning about our study. If yes, the healthcare team member will notify the research assistant who will explain the study to the child and parent/guardian. At the onset of this discussion, research staff will verify that the adult accompanying the child is the parent/guardian. Following the study explanation, all parents who remain interested in participating will be asked 21 screening questions to determine basic eligibility. Identifiable information will not be collected with exception of contact information. However, all identifying data will be removed if parents are not eligible or decide not to participate in the study. This screening is either in paper form or via secure UW Qualtrics application.

For those families who remain eligible after the basic screener, research staff will provide the parent/guardian as well as the child with the appropriate age-based consent/assent form and allow sufficient time for them to read it. As documented in detail in the application, standard IRB-recommended consent processes will be followed, including adherence to age-based recommendations for consent/assent.

For recruitment of current patients, we will send information about the study and an invitation to complete the basic eligibility screen either electronically (for those at UW who have previously provided consent to be contacted with research opportunities) or via US mail. The letter will contain the study information sheet and a secure link to UW Qualtrics link where they can complete the screening questions to determine basic eligibility. Those who do not have internet access can complete a paper copy of the

basic eligibility screener and return with a postage paid envelope, provided in our mailer.

With regard to flyers and notices, we will have a recruitment flyer to post in the clinic sites and on clinic websites. The flyer will provide contact phone numbers through which parents can request study information through email or regular mail. The research coordinator will get permission from the clinic administrator or web host to post the flyer.

Study Activities:
Screening for eligibility takes place at or up to 6 weeks before baseline data collection. Once determined to be eligible and informed consent is obtained, data collection elements and time points for usual care (U) and intervention (I) subjects proceed as in the timeline below.

Data collection for usual care (U) and intervention (I) groups						
	Baseline	Session 1	Session 2	Session 3	Session 4	6 month post	12 month post
Data Element	(0 months)	(3 months)	(6 months)	(9 months)	(12 months)	(18 months)	(24 months)
Glycemic control							
A1c	U, I	U, I	U, I	U, I	U, I	U, I	U, I
Fear of hypoglycemia	U,I		U, I		U, I	U, I	U, I
QOL							
Parent	U, I		U, I		U, I	U, I	U, I
Child	U, I		U, I		U, I	U, I	U, I
PRISM	U, I		U, I		U, I	U, I	U, I
Covariates							
Family characteristics	U, I				U, I		U, I
Disease and regimen factors	U, I				U, I		U, I

The first outcome of interest is *glycemic control,* measured by A1c and fear of hypoglycemia. A1c is routinely obtained during clinic visits by point of care A1c. This outcome measure is continuous, but values could also be used to understand whether diabetes control is adequate (A1c values meets American Diabetes Association criteria). Fear of hypoglycemia will be assessed with standard tools for the parent and the child (15 items, survey burden 3 minutes), when age-appropriate.[16, 17] The second main outcome of interest is *QOL*, for both the parent and the child. The child and parent will complete these survey items (survey burden 10 minutes).[18] For the child, we will assess diabetes-specific QOL, measured by the total scale score (33 questions).[19, 20] Although prior work with this instrument suggests children as young as 7 years can complete the survey unassisted, research staff will be available to read the questions to younger children as needed. We will supplement these measures with published items assessing school, work, and play activities (9 questions).[21] For the parent, the adult version of the Peds QL[TM] Family Impact Module (28 questions) will be used (e.g., impact of diabetes on daily household and work activities, family relationships, and social functioning).[22]

Surveys will also periodically assess change in barrier scores from the PRISM, as well as covariates such as demographics (e.g., child gender or household composition),

healthcare utilization (e.g., hospitalizations or provider visit type and date), comorbidities, and insulin regimen (e.g., pump or injection).

Information from Medical Records:
Families will be asked for consent to collect information from the child's medical record. This information would include demographics (e.g., gender, date of birth, zip code, or insurance provider), growth parameters (e.g., height and weight), healthcare utilization data (e.g., hospitalizations, healthcare provider visits, and names of providers), other comorbidities (e.g., celiac disease) and date of diagnosis, referrals to providers/resources (e.g., the diabetes educator or eye care), and insulin regimens, as well as lab orders and results (e.g., hemoglobin A1c, thyroid screening, urine screening, blood pressure, cholesterol, or celiac screening).

Data Collection:
We will screen possible participants to determine if they meet inclusion criteria. Once basic eligibility is determined and informed consent is obtained, we will administer a survey including the PRISM (Problem Recognition in Illness Self-Management) tool, as well as family characteristics, quality of life, fear of hypoglycemia, and disease management factors (for example, regimen and adherence). Family characteristics include parent/child age (continuous),[23-30] race/ethnicity, child gender,[23, 28] parent relationship to the child (mother, father, or other)[31] and household structure (single parent, two parent, or other),[1] parent education (standard categories),[31] primary diabetes provider, distance to care, disease and regimen factors including year of diagnosis, insulin regimen, and use of glucose monitoring technology, lifetime number of diabetes hospital days and hospitalizations, inventory of specific chronic illnesses (e.g., attention deficit/hyperactivity disorder, developmental delay, celiac disease, or asthma),[32, 33] and health status (single item, 5-point scale).[33, 34]

Statistical Considerations:
A first step in our analyses is the description of our data. Bivariate relationships will be assessed with measures of association such as correlations and regression coefficients for continuous variables and odds ratios for categorical variables. Ordinal and count variables will be collapsed into fewer categories if some levels are sparsely populated. We will undertake a full analysis of the level, reason, and impact of missingness. Several techniques will be applied to assess whether bias from missing data has occurred. These include multiple imputation[35] of missing data elements and pattern mixture models[36] to assess the impact of missed visits.

Analyses will model intervention outcomes with mixed effects models as:

$$g(y_{ft}) = (\beta_0 + a_f) + \beta_1 (Intervention)_f + (\beta_2 + b_f)(time)_{ft} + \beta_3 (Intervention \times time)_{ft} (+\varepsilon_{ft}) \qquad \text{(Equation 1)}$$

where g is a link function suitable to producing appropriate measures of the intervention's effect for the scale of the outcome y, t = time (t=0-X time points during or after the intervention), f = family (f=1…300 families), a_f and b_f are family specific random intercepts and slopes and ε_{ft} enters when equation 1 describes a mixed linear model.

The link function g will be chosen as the identity link for continuous outcomes (e.g., A1c), as the log for count variables, and as the logit for dichotomous variables. Time will be modeled in several ways: as indicator variables, as a pre-post intervention indicator, and as an ordinal indicator. Depending on results of these tests, the interventions' effect will be described for time points combined, as a trend, or at specific time points after initiation. The variance of random slopes and intercepts will be estimated to assess individual variation in time trends.

Covariates will be added to this model to increase precision and/or adjust for any imbalance between intervention arms as needed and will include an indicator for provider and family demographics. We will evaluate adding fixed effects for the site, although it is unlikely that this will significantly improve model fit as there is typically more variation between providers than between sites. All models will be constructed using Stata 12 (StataCorp, College Station, TX).

The study is powered to evaluate effects on glycemic control and quality of life (QOL), assuming a two-tailed alpha=0.05. We conservatively estimated values over time for an individual family would correlate at 0.08. Previous studies suggest moderate effect sizes (0.3-0.50; e.g., 0.-1.0% reductions in A1c or 6-9 point improvements in QOL) for the self-management resources used in this trial. Using a repeated measures approach and considering our outcomes as continuous, samples of 100 families per arm will provide 80% power to detect small to moderate effects (0.2-0.30) on glycemic control and QOL. Power calculations were conducted with PASS 2008. Based on pilot data, we estimate 70% retention of subjects in the trial. Thus, we will recruit 300 families.

Data Handling, Storage and Protection:
All research procedures will be conducted in private rooms or in a quiet corner of the waiting area, if preferred by families. The option of completing surveys and consent forms in the waiting room is offered because participating families have preferred to use their time in the waiting room in this manner, based on our prior work.

No serious risks are envisioned for subjects. A potential risk is the possibility of a subject's loss of confidentiality. Subjects are identified in research records indirectly. Information identifying subjects is linked to data record but stored separately. The research protocol is designed to minimize the risk of breach of confidentiality. Collection of identifiable or sensitive information is limited to that absolutely necessary for the research. All potentially identifiable electronic data will be stored (A) directly onto secure data servers hosted by Qualtrics (the UW-licensed web survey engine used to generate and administer the online version of our surveys), accessible only through UW NetID login by PI-designated members of our research team, (B) in password protected documents on data servers and workstations located behind UWSMPH or UWMF HIPAA-compliant firewalls, with access limited to research staff at the PI's instruction, and (C) on encrypted, password-protected external hard drives under double lock and key with access limited to research staff at the PI's instruction. All non-electronic data (some surveys, consent/permission forms) are stored under double lock-and-key such as in a locked drawer within a locked secure room.

In order to collaborate with individuals outside of the University of Wisconsin-Madison to conduct fidelity assessments for intervention group sessions, we will use the Department of Pediatrics Computer Services (Peds IT) Citrix remote access service. Citrix allows users with Pediatrics Active Directory accounts to access network file shares, applications, and a full Windows desktop environment. Authorized clients can securely authenticate with their centrally-managed Active Directory account and use the service from any network-accessible location, from any device that will run a supported Citrix client (Mac OSx, Windows, iOS and others). If the endpoint is not managed by Pediatrics IT, the client will not be allowed to move files between the Citrix network shares and the endpoint, ensuring that files are kept on our secure HIPAA-covered network. Project leaders will notify Pediatrics IT when accounts need to be created and when they are to be disabled. Usernames and temporary passwords are provisions by Pediatrics IT and communicated with the end user, who is prompted to create a new password on first login.

The only data stored on portable devices is data from audio recordings of the group intervention sessions. Additional safeguards are applied to protect these data from risk of breach of confidentiality. Group facilitators will audio record the sessions. The audio recording devices use a digital hard drive (no tapes) and will be stored in a locked cabinet in a locked room after each session. Although our pilot work suggests that these recordings do not typically contain identifiable information, research staff will review the audio recordings to make sure that material recorded is de-identified and then promptly transfer the recordings to the Pediatrics IT Citrix system. Research staff will then erase audio recordings on the devices. At the conclusion of the study, audio recordings will be destroyed by deleting the audio files from the Citrix system.

All research members will be trained regarding human subjects research using the standard, web-based CITI training modules and will possess appropriate HIPAA and human subjects protection certifications. The PI or the research coordinator is available either by pager or cell phone at all times for unanticipated problems or complications.

Data and Record Keeping:
The PI will oversee all study procedures, with the research specialists also overseeing the collection and storage of the data. As described previously, all potentially identifiable electronic data will be stored (A) directly onto secure data servers hosted by Qualtrics (the UW-licensed web survey engine used to generate and administer the online version of our surveys), accessible only through UW NetID login by PI-designated members of our research team, (B) in password protected documents on data servers and workstations located behind UWSMPH or UWMF HIPAA-compliant firewalls, with access limited to research staff at the PI's instruction, and (C) on encrypted, password-protected external hard drives under double lock and key with access limited to research staff at the PI's instruction. All non-electronic data (some surveys, consent/permission forms) are stored under double lock-and-key such as in a locked drawer within a locked secure room.

When completed, any such paper forms will be taken to the research office by research assistants immediately after each clinic session. The research assistant will check all forms for accuracy and completeness. Data from these forms will be entered by research assistants into the secure, Qualtrics application described previously. Range checks and consistency checks will be programmed to occur at data entry. Final data will reside in a Stata database with identifying information removed.

Data will be maintained by the PI as long as it proves to be useful for its stated purposes, and a minimum of 7 years from completion. At the appointed time for data destruction, identifiable data files will be deleted from the server and hard drives. Identifiable non-electronic data will be destroyed using the Department of Pediatrics-approved confidential document destruction service.

Monitoring and Addressing Potential Problems:
As described earlier, no serious risks are envisioned for subjects. A potential risk is the possibility of a subject's loss of confidentiality. As described above, the research protocol is designed to minimize the risk of breach of confidentiality. Should any such breach occur, study staff would notify the PI immediately. However, emotional distress can sometimes emerge over time. The research staff will notify the PI within 48 hours of any emotional distress experienced by a study subject and can also provide positive support and encouragement throughout the study to address any such issues. Of course, study participants experiencing emotional distress can discontinue study participation at any point of their choosing. Further, we have the ability to monitor quality of life for control and intervention subjects. Based on prior work with the study's quality of life instruments, a subject experiencing a 1 standard deviation decline in quality of life from baseline at any point in the study would prompt offering supportive care consultation within 48 hours with the clinic social worker or psychologist. Also, based on prior pilot work, we do not anticipate enrollment of subjects with significant substance abuse or mental health issues.

All research members will be trained regarding human subjects research using the standard, web-based CITI training modules and will possess appropriate HIPAA and human subjects protection certifications. The PI or the research coordinator is available either by pager or cell phone at all times for unanticipated problems or complications.

Collaborating sites:
The collaborating sites are Children's Hospital of Wisconsin (Milwaukee, WI) and Nemours Children's Clinic (Jacksonville, FL). The CHW site, under the direction of Dr. Fiallo-Scharer, will recruit and manage subjects for the trial. The Nemours site, under the direction of Dr. Wysocki, will provide consultation on study design as well as fidelity assurance for the intervention sessions.

Prior to trial recruitment, all UW and CHW investigators and research coordinators will be trained using standard protocols for all activities. Also, the investigators and research coordinators at UW and CHW will be in weekly email contact to discuss study status and address any regulatory or clinical issues that require attention. There will be

a weekly conference call between these two groups to monitor the study recruitment plan, informed consent process, study protocol compliance, data collection, and data security procedures.

Approximately once a month Dr. Cox (PI) will have a conference call with the co-investigator at CHW and Timothy Wysocki, PhD, co-investigator at Nemour's Children's Clinic whose role is that of a consultant on study design and on intervention fidelity. They will discuss study progress and group session implementation. Results of intervention fidelity will be shared and issues addressed as identified.

All external key personnel will be required to have appropriate certifications. Documentation of course completion will be stored the in UW study office.

If personnel at other sites believe that IRB protocol changes are needed, they will be instructed to communicate with the coordinating center regarding the desired change. The PI will make a determination as to the appropriateness of the proposed change. Any needed protocol amendment will be written by the PI and submitted to the IRB at the coordinating center. Any amended protocols approved by the IRB of record will be communicated to sites via above communication methods. In addition, to ensure each site's compliance to the protocol, a current hard copy or electronic copy of the protocol will be shared with all personnel. Each site's research coordinator will immediately replace previous protocol versions with any amended protocol approved by the IRB of record and communicate this to all investigators and research staff.

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