Protocol Title: Reducing hypoglycemia fear in parents of young kids with video-based telemedicine

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Current Research Design. The proposed study timeline is shown in Figure 1. We will recruit 48 parents of young children with T1DM (ages 1-6 years) from the Pediatric Diabetes Clinic at the Children's Mercy Hospital (CMH). *Inclusion criteria* are: age between 1-6 years, diagnosis ≥6 months, treatment with intensive insulin regimen (pump or MDI). *Exclusion criteria* are: parents of children on a conventional regimen and parents who do not speak English. If successful, a future trial of a Spanish version of RED CHiP would be developed. As of 05/2014, there are 138 families of young children with T1DM who receive care at CMH. Since 2010, there has been a consistent rate of new diagnoses in this age group of 25-30 children per year. The PI has averaged a 75% recruitment rate from the CMH clinic for projects recruiting families of young children. Thus, if she is able to maintain this rate, she would have about 120 families interested in participating in this project, of which only 48/120 are needed, suggesting successful recruitment if at least 40% of likely interested families enroll. *Procedure.* The study will use a randomized wait-list controlled design. The parent (mother or father) primarily involved in their child's daily T1DM management will be invited to participate with their child. We will plan to recruit 24 families to each of the immediate treatment and wait-list control groups (we will target at least 20 families per group to complete the study; 20% attrition rate). A member of the research team will identify families eligible to participate. Parents will undergo randomization after they provide written informed consent. We will stratify parents based on their child's gender and conduct random assignment to the two groups using blocks of four. We intend to recruit three family cohorts each consisting of 16 families (8, immediate treatment, 8 wait-list). We will instruct parents randomized to the wait-list control group to follow their physician's recommendations for their child's T1DM. Then, after the 14 week wait-list control period, we will invite parents in the control group to participate in RED CHiP. We will instruct parents randomized to the immediate treatment group to follow their physician's recommendations for their child's T1DM. In addition, they will receive 14 weeks of RED CHiP. Parents randomized to the immediate treatment group will also complete a follow up assessment, corresponding with the time when parents in the wait-list control group have finished the RED CHiP program (see Figure 2). Because we plan to use a mixed-method approach to evaluate the feasibility and acceptability of RED CHiP, we will also randomly sample 5 parents from both the immediate treatment and wait-list control groups (n=10 total) to complete a semi-structured qualitative interview. Parents will complete the interview at the time of their last assessment visit (e.g., followup, for parents in the immediate treatment group; post-treatment for parents in the wait-list control group). Parents will be able to complete all of the surveys online either with their own computer or an iPad 2 loaned to them by the study. A research assistant will work with parents to complete the online surveys, download children's glucometers and insulin pump, and collect a finger stick blood sample to measure children's Hemoglobin A1c (HbA1c) at each time point.

Figure 2. Intervention Timeline

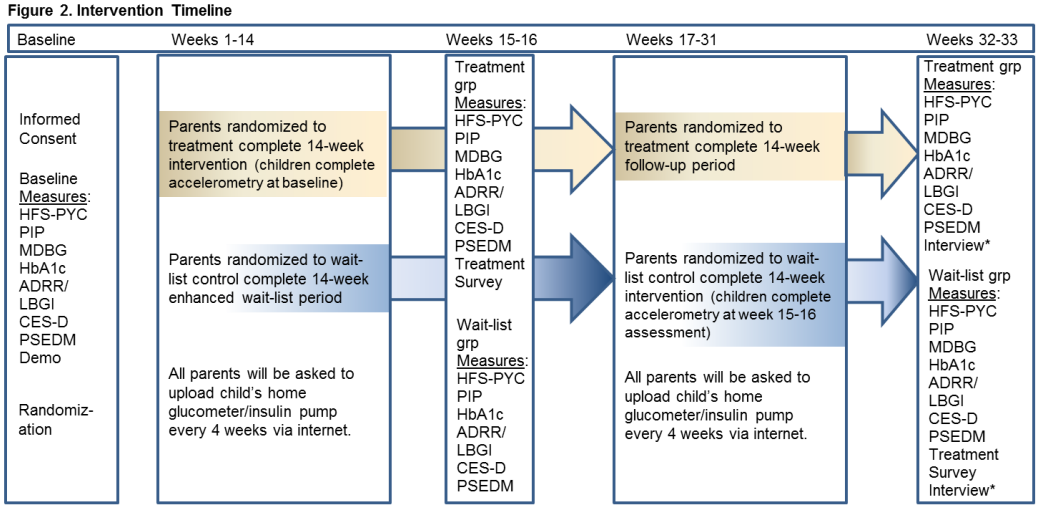

Figure 2. Legend. HFS-PYC: Hypoglycemia Fear Survey-Parents of Young Children; PIP: Pediatric Inventory for Parents; MDBG: Mean Daily Blood Glucose; HbA1c: glycated hemoglobin; ADRR: Average Daily Risk Range; LBGI: Low Blood Glucose Index; CES-D: Center of Epidemiologic Studies-Depression Screen; PSEDM: Parent Self-Efficacy for Diabetes Management; Demo: Demographic & Medical History Survey; Treatment Survey: Treatment Satisfaction Survey; *Semi-structured interview to assess feasibility/acceptability, conducted in random subset of families (n=10)

RED CHiP Treatment. The RED CHiP (Reducing Emotional Distress for Childhood Hypoglycemia in Parents) treatment is based on the PI's previous research[17, 25, 27] and the seven core concerns identified in a recent systematic review of parental FH[16]. We propose a treatment format that will alternate between group and individual telemedicine sessions. We will teach core intervention material during the group sessions, while we will use the individual sessions to tailor strategies for each family. Some examples of tailoring include using each child's personal accelerometer data to help parents identify behavioral patterns that may increase/decrease risk of hypoglycemia and reviewing each child's glycemic pattern to help parents see how over or under-treating for hypoglycemia may relate to daily glycemic control. The intervention will use a three-pronged approach to reduce parents' FH. It will leverage diabetes education and problem-solving to enhance parents' knowledge and skills. It will use behavioral parent training (BPT) to promote parents' skills and confidence in managing disruptive child behaviors and reducing their reliance on other hypoglycemia avoidance behaviors. Finally, it will apply cognitive-behavioral therapy (CBT) strategies drawn

from the anxiety literature to promote parental coping and self-efficacy and reduce parental fear and stress. Sessions will last about 60 minutes each. The primary interventionist will be a psychology postdoctoral fellow whom we will hire for the current project. He/she will use the RED CHiP treatment manual for sessions (see Appendix C) and will receive ~20 hours of training with the PI prior to the start of the intervention. The PI will also assume primary responsibility for on-going clinical supervision of the treatment sessions. We will measure fidelity to the treatment manual by comparing a digital video recording of the sessions to a check list of content items for each session. The video recording will be captured and stored via the videoconference bridge. A research assistant who is not involved in treatment delivery will complete the fidelity check for 33% of sessions. We will conduct the telemedicine sessions using the *Polycom RealPresence m500 app*. We selected this software system because it is reliable and viewable on multiple televideo devices (e.g., mobile devices and computers). The software is also uniquely geared toward group sessions because it can simultaneously display up to 10 different sites (i.e., parents) or a powerpoint presentation on a mobile device or computer screen (e.g., like the tiled opening credits of the 1970's Brady Bunch TV show). Families will use the Polycom software to access KUMC via one of our existing videoconference bridges. These bridges provide a secure and confidential connection to KUMC and are fully HIPAA compliant. Although the Polycom software is viewable on a computer or mobile device (i.e., iPod Touch, iPad, smart phone), we will, as needed, loan families an iPad2 tablet with data plan (16GB, WiFi and 3-G-enabled; Apple, Inc.) to use for the duration of the study. All of the iPad2 tablets used in this study will include tracking software to discourage theft. Parents receiving a loaned iPad2 will need to sign the standard KUMC iPad loan agreement for research (see Appendix D). In the past, colleagues who have used these procedures when loaning out devices (e.g., computer, tablet) have reported a high recovery rate (95% total recovery rate; ~80% if we exclude damaged iPads). At the end of the study all iPad2 tablets will be returned to the research staff. Of note, families owning their own camera-enabled iPad/computer and with internet access may be able to participate using their own devices. Based on the PI's research, 95% (136/143 families) of parents of young children with T1DM report access to a computer with an internet connection. If we estimate that 80% of these families will also have an internet-enabled device with a camera, then it is possible that our actual rate of iPad2 loaning may be low (we estimate 12 families).

Orientation. A trained research assistant will conduct orientation visits following randomization for families in the immediate treatment group and the wait-list period for families in the wait-list control group. These visits will include training on how to use the iPad and *Real Presence m500 app*.

Accelerometer. During RED CHiP, children will wear an accelerometer (Actigraph GT3X) for at least 5 days to measure their typical daily physical activity (PA). In young children, the link between glycemic response and PA remains unclear. Accelerometer data will provide an accurate measure of children's PA, since research shows that parents often underreport their child's engagement in unstructured PA.[41] Children's total daily PA (total movement counts/total measurement time in minutes) will be calculated as well as a diagram of their typical daily PA patterns. We will use these data to educate parents regarding the relationship between their child's activity patterns and blood glucose levels. We expect that giving parents specific strategies for insulin dosing and carbohydrate intake in the context of their child's typical PA routine will improve parents' T1DM management and children's glycemic control.

Wait-list Control. After randomization, families assigned to the wait-list control condition will receive a copy of the clinics' standard flow sheet for the treatment of hypoglycemia. Families will cross over to the treatment arm at the end of the 14-week wait-list period.

Outcome Measures. Primary outcome measures will be: parents' FH, parenting stress, children's glycemic levels (measured using mean daily blood glucose levels and HbA1c), and children's glycemic variability (measured using the average daily risk range and the low blood glucose index). Secondary outcome measures will be the Feasibility and Acceptability of RED CHiP. Covariates for these pilot analyses will be parents' depressive symptoms and child age (see Table 3). If more than one parent participates in RED CHiP, we will use the data from the parent who self-identifies as the most responsible for their child's T1DM management in the study analyses. If parents indicate equal responsibility, we will collect data from both parents for each time point and we will average both parents' data for the analyses.

Data Management and Statistical Analyses. Parents will input their data into a RedCap database accessible via the internet. Missing data for continuous variables that cannot be recovered from parents will be imputed using either subscale or total scale mean score substitutions (e.g., HFS-PYC, PIP, CES-D). Again, covariates for Hypotheses 2a-b and 3a-b will be parents' depressive symptoms (DS), and child age (AGE).

Hypotheses.
Hypothesis 1: RED CHiP will be feasible and acceptable to families of young children with T1DM.

Hypothesis 2a and b: Parents who receive RED CHiP will have a reduction in fear of hypoglycemia (HFS-PYC) and parenting stress (PIP) as compared to the wait-list group (*Hyp 2a*) and pre-RED ChiP measures (*Hyp 2b*). *Hypothesis 3:* Children whose parents receive RED CHiP will experience an improvement in mean glycemic levels (MDBG & HbA1c) and variability (ADRR & LBGI) as compared to the wait-list group (*Hyp 3a*) and pre-RED ChiP measures (*Hyp 3b*).

Power analysis. This is a pilot and feasibility study with the purpose of generating data to support a full, randomized controlled trial. Power analysis of a test of the difference between pre- and post-HFS-PYC with a 10% decline in survey scores (i.e., from M=78.6± 18.4[17] to M=71) yielded a power of 84%, while a 15% decline in PIP-F scores (i.e., from a M=107.2±32.6[27] to M=91) yielded a power of 92% when n=40, α=0.05 for both tests. Repeated measures ANCOVA (RM-ANCOVA via GLM) yielded a power of 92% and 82%, respectively, for 10% declines in parents' HFS-PYC and PIP-F scores. When using RM-ANCOVA and assuming a 10% decline in children's HbA1c, tests yielded 95% power when n=40 and α=0.05 (M=8.8±1.5% to 8.0%). Assuming an attrition rate of 20%, we will need to recruit 48 parents (24 per group) to ensure we have ≥40 parents with post-treatment data. This sample size is also sufficient to estimate effect sizes for the study outcomes.

Data Analysis. We will first run descriptive statistics and statistical distributions for all measured variables at baseline (B), weeks 15-16 (w15-16), and weeks 32-33 (w32-33). We will conduct sensitivity analyses for all primary outcomes to evaluate any effects due to attrition. We will also use an intent-to-treat analysis strategy, wherein we will use an imputation model to examine participant data even if they are lost to attrition.

Hypothesis 1: (Quantitative data): We will assume feasibility if families' mean group session attendance is ≥70% and participant attrition is ≤20. We will assume acceptability if parents' mean scores on the Treatment Satisfaction Questionnaire are ≥65. *(Qualitative data):* We will use Framework Matrix Analysis (FMA) initially. FMA is an efficient approach to qualitative data analysis where data are analyzed using themes derived *a priori* instead of *de novo.*[52] *A priori themes* will be based upon the interview agenda (viz., strengths, weaknesses, ways to improve RED CHiP and overall study feasibility). Thus, use of FMA will allow refinement of RED CHiP within the limited timeframe of the R21 mechanism. We will apply a grounded theory approach to analyze transcripts upon completion of all interviews. This more comprehensive approach will allow for identification of *de novo* themes, which will be integrated into RED CHiP protocols and submitted for publication.[53, 54]

Table 3. Planned Assessment Measures

	Measure	Description
PRIMARY MEASURES:	Hypoglycemia Fear Survey (HFS-PYC)	26-item parent-report of fear of hypoglycemia; reliable and psychometrically sound for use in young children with T1DM;[17,25] we will use the Total Score, measuring both worry and behavior related to hypoglycemia prevention
	Pediatric Inventory for Parents (PIP)	42-item measure of parenting stress; reliable and psychometrically sound for use in parents of young children with T1DM;[27,42-43] we will use the Frequency (PIP-P) and Difficulty (PIP-D) scores
	Mean daily glucose (MDBG)	14-day glucometer downloads; we will use data for the 2 weeks preceding each assessment point
	Hemoglobin A1c (HbA1c)	Proxy measure of average glucose control; will be measured by automated high performance liquid chromatography (reference range: 4.0-6.0%, Tosoh 2.2, Tosoh Corporation, San Francisco, CA); measurement method is reliable to DCCT standards;[44] all HbA1c will be measured by a central laboratory at CMH; CMH has recorded excellent reliability between preserved fingerstick and fresh venous blood samples (r=0.98)
	Average Daily Risk Range (ADRR)	A measure of risk of glycemic variability;[51] scores are calculated based on a minimum of 14-days of self-monitoring blood glucose (SMBG) data; scores >40 suggest a high risk for variability; has been used previously in young children;[35] our pilot data show a correlation between children's ADRR scores and percent of low blood glucose values (r=0.93, p=0.03)
	Low Blood Glucose Index (LBGI)	A measure of risk for a low blood glucose level;[45] based on a normalized transformation of SMBG to remove bias due to the natural asymmetry of blood glucose (greater range of hyper versus hypoglycemic levels); LBGI is based on a minimum of 14-days of data; sensitive to hypoglycemic events only; our pilot data show a correlation between children's LBGI and percent of low blood glucose values (r=0.88, p<0.001)
SECONDARY MEASURES:	Feasibility (Quantitative)	Feasibility of RED CHiP will be based on attendance to group sessions ≥70% and attrition ≤25%
	Acceptability (Quantitative)	Acceptability of RED CHiP will be based on our Treatment Satisfaction Questionnaire, a 16-item measure; the Treatment Satisfaction Questionnaire will use a 5-point Likert scale to assess perceived acceptability of the RED CHiP content and structure (mean score ≥65, range: 16-80)
COVARIATES:	Demographic & Medical History	Family/child characteristics; medical history; T1DM events; we will collect this during the baseline assessment; child age will be used as a covariate
	Center for Epidemiologic Studies-Depression Scale (CES-D)	20-item self-report;[47] reliable in parents of children with T1DM;[29] superior to Beck Depression Inventory in identifying depressive symptoms in T1DM;[46,48-49] Total Score will be used as a covariate; higher values suggesting greater frequency of depressive symptoms

Note. Please see Appendix A for sample questions from each measure.

Hypotheses 2a and b: We will score outcome measures as continuous variables with within-group standardized effect sizes (in SD units) and within-group changes for FH (HFS-PYC) and parenting stress (PIP-F and PIP-D) calculated based on parents' B, w15-16, and w32-33 scores. To test for between-group differences on parents' FH and stress at B, w15-16, and w32-33, we will use both repeated measures ANCOVA (RM-ANCOVA) and a 2x2 factorial (condition x time) MANCOVA. We will also use these to test for *within-group x time* differences. Our covariates will be AGE and DS.

Hypotheses 3a and b: We will calculate within-group standardized effect sizes (in SD units) and within-group changes for children's glycemic levels and variability based on children's B, w15-16, and w32-33 values. As in Hypothesis 2, we will employ General Linear Models (GLMs) such as RM-ANCOVA and a 2x2 factorial (condition x time) MANCOVA to test for between-group differences on children's glycemic levels (MDBG & HbA1c) and variability (ADRR & LBGI) at B, w15-16, and w32-33 and for *within-group x time* differences. Our covariates will be AGE and DS.

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