Fixed dose for Fixed Carbohydrates vs. Variable Dosing for Variable Carbohydrates: A Study of Rapid-Acting Mealtime Insulin in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus

Date: October 16, 2019.

NCT # NCT04157738

1. TITLE PAGE

Fixed dose for Fixed Carbohydrates vs. Variable Dosing for Variable Carbohydrates: A Study of Rapid-Acting Mealtime Insulin in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus.

Eric I. Felner, MD, MS *
Jacqueline V. Reyes Diaz, MD **
Courtney McCracken, PhD***
(*) Professor of Pediatrics, Division of Pediatric Endocrinology, Emory University.
(**) Fellow, Pediatric Endocrinology, Emory University.
(***) Pediatric Biostatistics Core, Department of Pediatrics, Emory University

Version Date: October 16, 2019.

2. EXTERNAL COLLABORATERS

Not applicable

3. ABSTRACT

Type 1 diabetes mellitus (T1DM) is a challenging medical disorder, especially in children and adolescents. In order to prevent the chronic complications of hyperglycemia, the maintenance of near-normal glycemic control must be balanced with minimizing hypoglycemia [1]. Prior to the 21st century, most individuals were treated with consistent carbohydrate intake and relatively set, or fixed doses of insulin [2]. Over nearly the past twenty years, with the availability of multiple rapid-acting and basal insulin analog preparations, individuals with diabetes have had the ability to utilize a variable carbohydrate and insulin regimen. These diabetics have the ability to eat as much or as little amount of food he/she desires, assuming he/she delivers an appropriate amount of rapid-acting insulin to cover the amount of carbohydrates. The insulin-to-carbohydrate ratio (ICR) is determined through trial-and-error as well as experience [3]. In addition to the use of the ICR, the management of diabetes for most children and adolescents requires consistent parental involvement and supervision [4]. Although children and adolescents with T1DM have much more freedom with the amount of food (carbohydrates) they eat while using an ICR at mealtime, the difficulty in determining the amount of insulin needed, how and when to adjust the ICR, the difficulty with understanding the basics of managing T1DM, and the adaptation to a new lifestyle with T1DM may be more complicated than utilizing a simple plan that includes a fixed amount of insulin and fixed number of carbohydrates, at least for the first few months after diagnosis. As complicated as it is for children, adolescents, and their caregivers to learn how to manage T1DM after being discharged home in usually < 48 hours after diagnosis, a more simplified insulin regimen at mealtime may provide the family of and the child or adolescent with newly diagnosed T1DM with less stress and anxiety while still maintaining adequate glycemic control.

Although many pediatric endocrinologists provide an ICR plan for their newly diagnosed patients with T1DM, fixed dosing and other forms of insulin delivery are available. The objective of this investigator-initiated, prospective proposal is to determine if children and adolescents with T1DM have improved glycemic control and, their families experience less anxiety with a fixed insulin and carbohydrate regimen compared to those using an ICR and variable carbohydrate intake.

4. BACKGROUND

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by a severe deficiency or absence of endogenous insulin, resulting in chronic hyperglycemia. The achievement of optimal glucose control is facilitated by intensive insulin treatment [5]. The current recommendations are based on the basal bolus

paradigm, with subcutaneous long-acting insulin or continuous subcutaneous infusion of rapid-acting insulin to cover basal requirements and with rapid-acting insulin to prevent or correct glucose excursions. Home blood glucose monitoring has been the mainstay for glucose monitoring for more than 30 years. It provides information about an individual's glucose level and allows individuals to make adjustments as needed to help them manage their glycemic control [6].

Despite advances in medical treatment and technology, nutritional therapy continues to be the cornerstone of diabetes management [7]. Carbohydrates are a major determinant of postprandial blood glucose. Carbohydrate counting is a meal planning approach that focuses on carbohydrates as the primary nutrient affecting postprandial glycemic response. Advanced carbohydrate counting allows adjustment of the prandial insulin dose for actual carbohydrate intake for diabetics using intensive insulin therapy. According to the Bell and Shimin meta-analysis, carbohydrate counting significantly reduced HbA1c concentration in adults [8,9]. Tascini et al reported that carbohydrate counting had a positive effect in children and adolescents with T1DM, by reducing hypoglycemic events and improving quality of life [5]. These studies, however, did not compare different types and amount of insulin for variable carbohydrate intake.

Fixed mealtime carbohydrate with a fixed mealtime insulin dose is a simplified regimen that provides a set amount of insulin for a set amount of carbohydrates and ensures that each dose and each meal is consistent. A set amount of carbohydrate is assigned in grams or portions and patients choose different carbohydrate servings to equal the target amount. This method is easy to use and may be appropriate for patients who are new to taking insulin in that it may improve compliance, glycemic control, and anxiety.

Shortly after diagnosis of T1DM, many children and adolescents not uncommonly experience a honeymoon period [10]. It occurs because there is a sufficient amount of residual B-cell mass that enables some of these individuals to secrete some endogenous insulin. As a result, in order to prevent hypoglycemia, these individuals may be managed with less exogenous insulin over a short period of time [11]. This variability makes less accurate HbA1C concentration as a gold standard for assessing glucose control in the first 6-12 months after diagnosis [12,13].

Glycemic variability (GV) obtained from multiple blood glucose levels (up to 6 – 10 times/day) provides a good correlation for an individual's glycemic control and predictor of chronic diabetic complications [3]. The GV refers to swings in blood glucose levels and captures blood glucose oscillations that occur throughout the day, including hypoglycemic periods, postprandial increases, as well as blood glucose fluctuations that occur at the same time on different days [14]. The proposed target range of 70–180 mg/ dl is considered acceptable for clinical practice, as it has been observed that if 50% of the self-monitoring of blood glucose readings are in this range, the A1C would be ~7% [12,13]. Shapiro et al, reported that teens and parents show some similarities in the facets comprising distress, including negative emotions about diabetes and the demanding diabetes regimen [15]. Simplified insulin treatments will remarkably help to maintain adherence and to prevent deterioration in glycemic control.

For the purposes of this study the following definitions will be used:

BMI: Weight (kg)/ Height (m2).
Glycemic variability: Blood glucose oscillations that occur throughout the day. The glycemic range on target is between 80 – 180 mg/dl.
Insulin dose adjustment: Titration of insulin over time to improve glycemic control.
Parental stress: Stress associated to caring for a child with diabetes.
Insulin to carbohydrate ratio (ICR): Number of carbohydrates that 1 unit of rapid-acting insulin covers.
Basal insulin: Insulin that controls blood sugar consistently for 24 hours.
Rapid-acting insulin: Mealtime insulin. Typically has onset in 10 - 15 minutes, peaks at 45 – 60

5. APPROACH –RESEARCH METHODS

A. STUDY DESIGN

Two - Arm, Randomized, Clinical trial (See Figure 1)

This proposal is designed to compare children and adolescents with newly diagnosed T1DM using a fixed insulin dose for fixed carbohydrate mealtime regimen (FIXED group) to children and adolescents with newly diagnosed T1DM using an ICR with variable carbohydrate intake (ICR group) mealtime regimen and determine:

1) Specific Aim 1

Determine the feasibility for a subsequent clinical trial involving rapid acting insulin dosing for a fixed dose for fixed carbohydrates (FIXED group) vs ICR with variable carbohydrate intake (ICR group) in order to determine the capacity for recruitment, caregiver consent to random assignment and completion of study measures, average session attendance, caregiver treatment adherence, and post-treatment satisfaction.

2) Specific Aims 2

a) Determine if the caregivers of diabetics using a fixed insulin for fixed carbohydrate regimen (FIXED group) experience less anxiety than the caregivers of those using an ICR with variable carbohydrate intake regimen (ICR group) at 1- and 4-months post-randomization.

b) Determine if diabetics utilizing a fixed insulin for fixed carbohydrate regimen (FIXED group) have decreased glycemic variability (GV) than those using an ICR with variable carbohydrate intake regimen (ICR group) at 1- and 4-months post-randomization.

We hypothesize that we will recruit and consent enough patients in order to perform a future, larger trial where caregivers of children and adolescents with newly diagnosed T1DM using a fixed insulin for fixed carbohydrate mealtime regimen (FIXED group) will experience less anxiety and their diabetic children will experience less GV than children and adolescents with newly diagnosed T1DM who use an ICR with variable carbohydrate intake at mealtime (ICR group). If this proves to be true, less anxiety may encourage more compliance and better glycemic control.

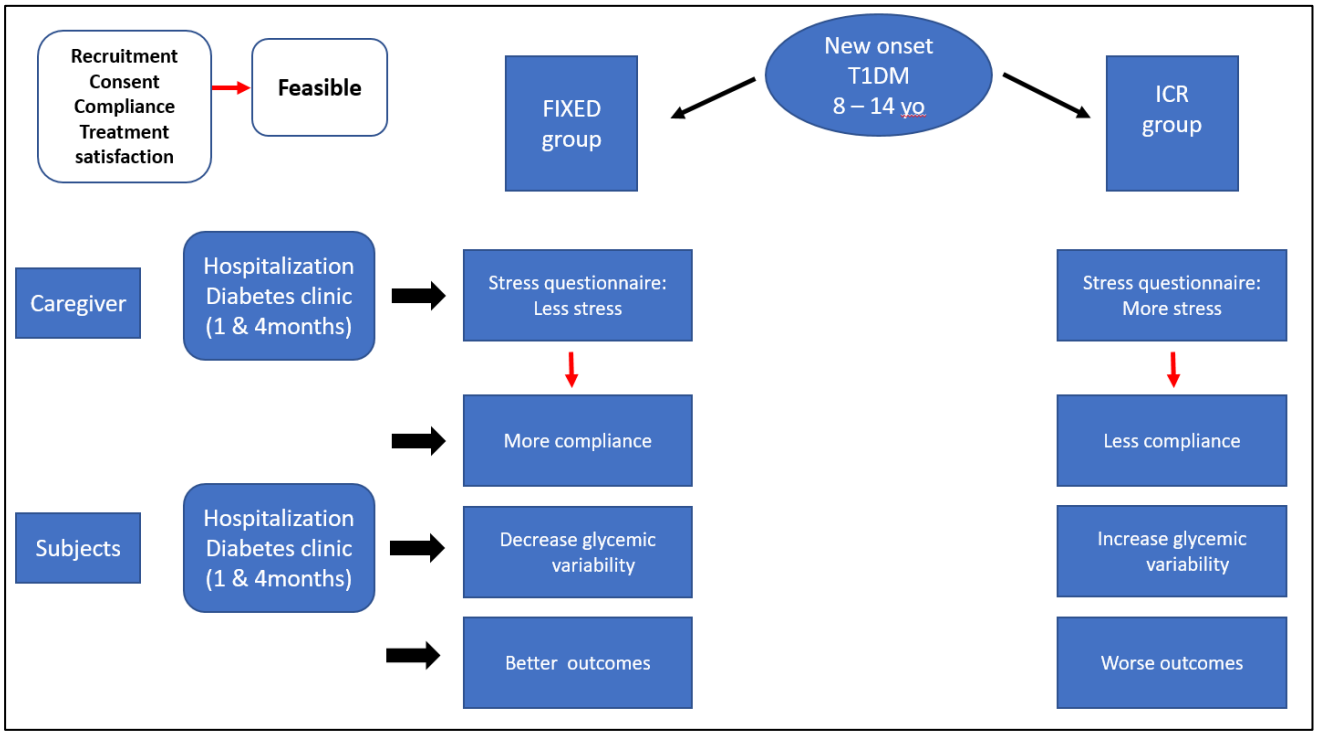

Figure 1: Study design and hypothesis.

3) Methods

a) Recruitment & Consent

Subjects with newly diagnosed T1DM will be evaluated by authorized study personnel under a HIPAA waiver to determine potential eligibility. The subjects will be contacted by the research study team while in the hospital during his or her initial diagnosis to explore his/her interest in the study and to confirm eligibility. The informed consent/assent documents will be signed at the time of the initial contact.

b) Initial Visit (at CHOA-Egleston)

Recruitment of the 20 to 40 pediatric subjects will take place at the Children's Healthcare of Atlanta at Egleston, when they are hospitalized with the diagnosis of new onset T1DM.
Enrolled participants will be interviewed in order to collect demographic information. The subjects will be randomized to either the FIXED group or the ICR group according to a computer-generated random sampling table. The subject and his/her caregivers will receive diabetes education while in the hospital in standard fashion. The subject and his/her caregivers will receive glucose monitoring education and training prior to hospital discharge. The subject and his/her caregivers will also receive a paper log to record the blood sugars, number of carbohydrates consumed, and insulin administered at each meal throughout the day.

Prior to discharge, all subjects will receive a regimen that includes a: 1) Meal-time insulin and carbohydrate regimen (# of units of insulin, # of carbohydrates, and/or ICR);

2) Evening dose of Glargine; 3) Hyperglycemia correction regimen for blood glucose levels > 199 mg/dL; and 4) Hypoglycemia treatment regimen for blood glucose levels < 70 mg/dL and/or symptomatic.

c) After Hospital Discharge and Between Clinic Visits

As per standard diabetes care, caregivers will report all blood glucose levels every day (to the study investigators) until the subject's initial clinic visit 4-6 weeks after diagnosis. All insulin adjustments will be made by the study investigators.

After the subject's first clinic visit, caregivers will contact the study investigators once a week to report blood glucose levels and the investigators will make adjustments as needed.

d) Diabetes Clinic Visits

All the diabetes clinic visits will occur at the Center for Advanced Pediatrics (CAP), approximately three miles from CHOA-Egleston Hospital. Subjects will attend clinic with one or more of the investigators approximately 1 and 4 months after enrollment.

At each clinic visit, subjects and their caregivers will answer standard diabetes questions, undergo a physical examination, and objective data (vital signs, glucose meter (GM) data, insulin dosing, and carbohydrate intake) will be collected by the study personnel.

B. STUDY POPULATION

The plan is to enroll from 20 to 40 children and adolescent subjects with newly-diagnosed T1DM. Twenty will be randomized to the FIXED group and twenty will be randomized to the ICR group. The subjects will be selected from children and adolescents admitted to CHOA-Egleston with a diagnosis of new-onset Diabetes Mellitus. Participation in this study will be determined by a set of inclusion/exclusion criteria.

1) Inclusion Criteria

For enrollment in the study, subjects must: (1) Have Confirmed diagnosis of T1DM based on the most recent ADA criteria [16]; (2) Be 8 - 14 years of age; (3) Begin monitoring with a glucose monitor prior to discharge from the hospital; and (4) Have the ability to understand and be willing to adhere to the study protocol. (5) English or Spanish speakers.

2) Exclusion criteria

For enrollment in the study, subjects may not: (1) Have a clinically significant major organ system disease (i.e., hypertension, hyperlipidemia, or obesity); (2) Be on glucocorticoid therapy; (3) Have Type 2 Diabetes Mellitus; (4) Have Polycystic Ovarian Syndrome (PCOS); (5) Have a BMI > 85^{th} %ile; (6) Have Acanthosis Nigricans; (7) Have any form of renal impairment; (8) Have Cystic Fibrosis; (9) Have Glucocorticoid-, Chemotherapeutic-, or any other Medication-induced form of Diabetes; (10) Be using any basal insulin other than Glargine insulin; (11) Have cognitive impairment (> 2 grades behind age-appropriate grade in school); (12) Be in Foster Care; (13) Have any history of DFCS involvement; and (14) If female, be pregnant or breast-feeding.

C. DATA MANAGEMENT

All data, including patient demographics, history, and laboratory tests will be collected on standardized forms and entered into an electronic database, REDCap. REDCap is a HIPPA-compliant, web-based, data capturing tool used in over 130 countries. Features include user-specific credentials, data-logging, longitudinal data modeling and more. Enrolled patients will be assigned a study ID. Subjects will only be identified in REDCap by their study ID. The patient's name, MRN and study ID will be kept in a secure file in a double lock in a filing cabinet under Dr. Felner's supervision in the Emory Children's Center. Records will be maintained for 10 years as required for IRB studies.

D. OUTCOME MEASURES

1) Primary Outcome Measures

The primary goal of this study is to determine the feasibility of a subsequent clinical trial of rapid acting insulin dosing for fixed carbohydrates (FIXED group) vs ICR with variable carbohydrate intake (ICR group). In doing so, we will examine our ability to recruit and consent patients (>70% consent rate), study retention (>90% retention), completion of study visits (average session attendance ≥ 90%), study measures (≥ 90% measure completion), caregiver treatment adherence, and post-treatment satisfaction (≥ 90%),

2) Secondary Outcomes Measures

Secondary outcome measures will include caregiver anxiety and glycemic variability. Each of these measures are described below.

One secondary outcome measure is caregiver anxiety. This will be assessed by a parental stress scale [17]. The caregiver will fill out the questionnaire at initial enrollment (prior to hospital discharge) and at each clinic follow-up throughout the study. We will use the Spanish adaptation of parental stress scale (PSS) [18] for Spanish population if necessary.

We clarify in the survey that the questions are to be answered in terms of how the caregiver-child relationship exists since the diagnosis of diabetes mellitus.
The scales are shown in **Annex 1 and 2**

Glycemic variability (GV) is another secondary outcome measure. The GV will be calculated in all subjects through the use of a glucose monitor (GM) data classification scale. Subjects will be considered to have appropriate GV if their blood glucose level is in the range of 80 mg/dL – 180 mg/dL (Group C).

The GV classification is as follows:
Group A: < 50 mg/dl.
Group B: 50 – 79 mg/dl
Group C: 80 – 180 mg/dl
Group D: 181 – 350 mg/dl
Group E: > 350 mg/dl

Safety is the last secondary outcome measure. The safety measured that will be compared in both groups include death, risk of life threatening event (i.e., severe hypoglycemia associated with seizure or altered mental status), hospitalization for diabetes complication (diabetic ketoacidosis or hypoglycemia), and risk of disability or permanent damage.

E. STATISTICAL CONSIDERATIONS

Randomization

Randomization will be performed by study statistician using random-permuted blocks of size 2 and 4. Randomization assignments will be placed in sealed, opaque envelopes to be stored. Study investigators will not be blinded to treatment assignment.

Sample Size

A goal of 20 patients is necessary for this study, but we will reach up to 40 participants in case there is any withdraw after consented and randomized. While the overall goal of the study is to demonstrate feasibility of a subsequent randomized controlled trial, limited efficacy testing will be performed. Given a sample size of 20 participants (10/grp), we will have greater than 90% power to detect a minimum standardized mean difference of 1.25 (i.e., approximately a 1.25 standard deviation difference) between groups. Effect sizes will be calculated for all study measures of interest and be used in future power calculations. On average, there are ~25 new type I/II diabetics diagnosed at Egleston hospital each month. Assuming an eligibility rate of 40%, 10 patients would be eligible to participate each month. Based on this, we are confident in our capacity to recruit 20 to 40 participants during the study period with the goal of having 20 participants to complete the study.

Statistical Analysis

Demographic characteristics will be summarized for both groups using means and standard deviations, medians and quartiles, or counts and percentages, as appropriate based on distribution. T-tests, Wilcoxon rank sums, and/or Chi squared tests will be used to assess differences between the two groups.

Primary Aims: Measures of feasibility (consent, retention, engagement, satisfaction, etc.), will be summarized overall and by group, when applicable.

Secondary Aim 1: Parental stress scale

The parental stress scale will be scored per the instrument's instructions. The total scores for the treatment groups will be compared in a cross-sectional fashion using t-tests or Wilcoxon rank sums tests as appropriate based on the distribution of scores. Changes in parental distress over-time will be evaluated using two-way repeated measures analysis of variance models. Models will include the main effect of treatment assignment, time (baseline, 1 month, 4 months), and the treatment X time interaction. The interaction term will serve as the primary statistical test for aim 2. Summary statistics, statistical significance, and effect sizes will be reported by group at each time point of interest, when applicable.

Secondary Aim 2: Glycemic variability

Glycemic variability will be examined both as a continuous variable and a categorical variable using the ranges defined in section D. Time series analysis will be used to examine daily measures of blood glucose (obtained from patient diary's) during the study period. Variability will be measured as the probability of acute change (PAC), using methods described by Jahng et al. (2008). Acute changes will be adjusted for time between readings. In addition, first-order autocorrelations and/or mean-square successive difference will be used to examine variation in readings as described by Janhg. Multilevel modeling will be used to test between-group differences in variability.

Secondary Aim 3: Safety

Adverse event of interest and serious adverse events (see section D) will be summarized overall and by treatment group. For participants experiencing more than 1 episode of a specific event (e.g., severe hypoglycemia), the maximum grade and severity will be recorded. Chi-square tests will be used to compare the frequency of events between the two cohorts.

Given the exploratory nature of these secondary outcomes, we will calculate effect sizes based on the adjusted means and standard deviations or differences in proportions, when appropriate.

All analyses will be conducted using SAS v9.4 (Cary, NC).

F. ANTICIPATED RESULTS

This research will be feasible to develop a successful larger clinical trial. Due to the fixed regimen seeming to be less complicated, because there are less calculations to make than in those using the ICR group, we anticipate that parental anxiety will be decreased in the FIXED group. This will encourage more blood glucose monitoring and treatment compliance. Therefore, we anticipate GV to be decreased for the FIXED group.

G. LIMITATIONS

The major limitations of this study are related to caregiver's self-completion questionnaire and ability to contact study personnel frequently during the study period in order to report blood glucose levels and implement the insulin adjustments. More than likely, multiple insulin regimens should work, but the idea behind this study is that the fixed regimen may be easier to implement.

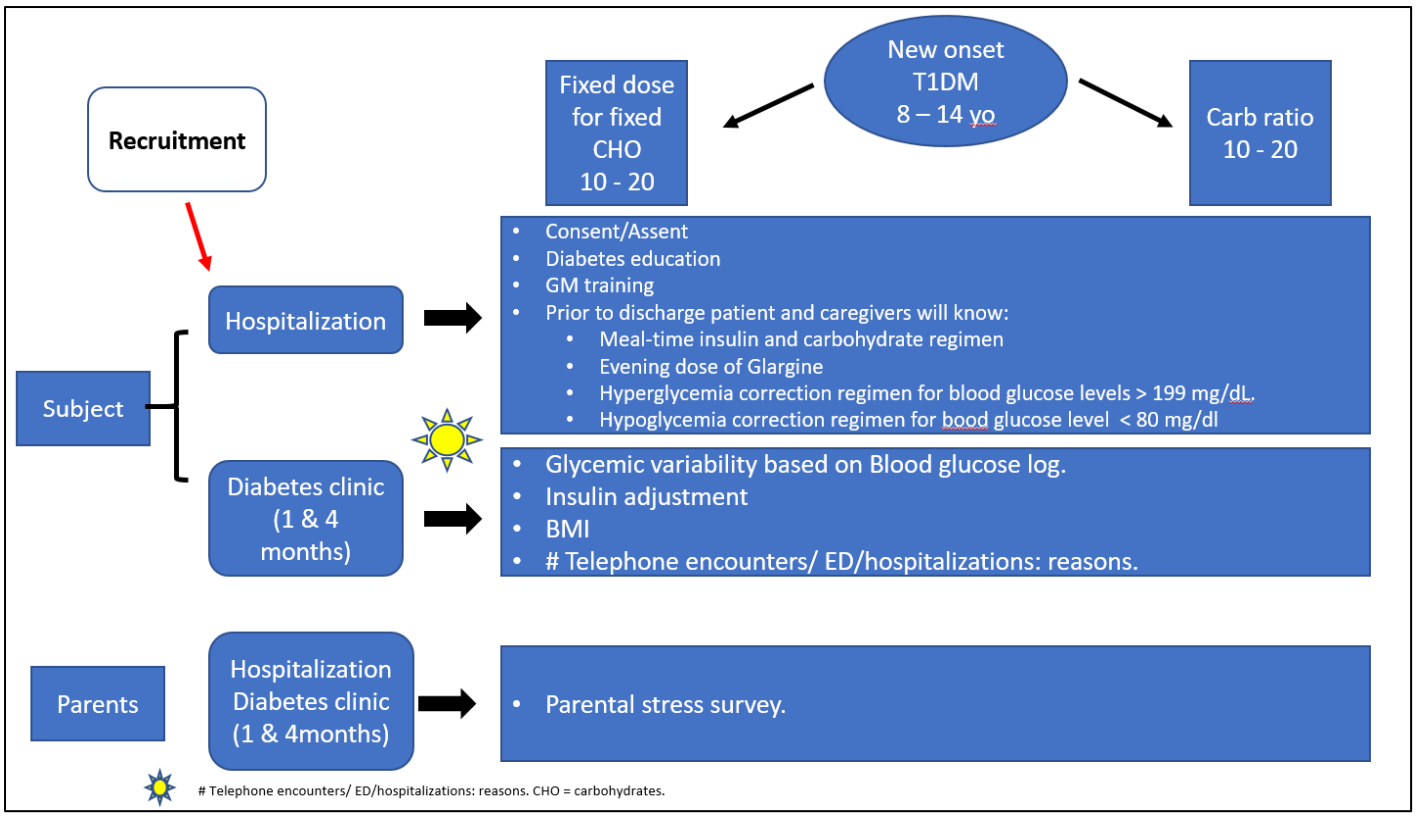

Figure 2: Proposed protocol.

6. DATA COLLECTION FOR FUTURE RESEARCH

Records will be maintained for 10 years as required IRB studies.

7. COMMUNITY PARTICIPATION

Not applicable

8. PARTICIPATION SELECTION

Study subjects will be selected from the cohort of pediatric patients with newly diagnosed of type 1 diabetes mellitus hospitalized at Children's Health of Atlanta and followed at diabetes clinic in the Center for Advanced Pediatrics Georgia. Parents will consent and subjects will assent for the subject to enroll in the research study.

9. INFORMED CONSENT

During hospitalization for newly diagnosed of type 1 diabetes mellitus. The study will be initially discussed, parents and participants will be provided with a HIPAA compliance form and consent/assent form.

10. INCIDENTAL FINDINGS

Not applicable

11. COMPENSATION FOR TIME & EFFORT

No monetary compensation will be provided to participants. Participants will not be charged for any of the research activities.

12. DATA & SAFETY MONITORING PLAN (DSMP)

There will not be an independently constituted data safety and monitoring board for this protocol because it does not involve an experimental intervention. Instead, this study will have a data safety and monitoring plan (DSMP). This plan includes examination of consent rates, attrition, and safety related data. The plan will be generated by the study statistician in conjunction with the PIs of the study. Presentation of data will be presented in a blinded fashion with treatments de-identified. The first DSMP will be reviewed after 12 patients enroll in the study, then subsequently every 6 months of the study. There are no plans for an interim analysis as this is a pilot study.

All relevant adverse events related with diabetes will be documented and reviewed by the principal investigator. These will be enumerated and reported according to IRB policies. Any serious adverse events will be reported within 24 hours to the IRB. They will be reviewed by all investigators and a disposition determined before proceeding with further enrollment. There are no additional laboratory evaluations outside of the routine care for patients with diabetes mellitus.

The procedures associated with this research trial are associated with minimal risk.

13. POTENTIAL BENEFITS

Participation in this study offers appropriate plans that are well-established and have been utilized to help children and adolescents with T1DM maintain appropriate glycemic control. Although the research may not benefit the subject initially and directly, the results of the study could lead to develop bigger clinical trial to demonstrate alterations of current management options for children and adolescents with newly-diagnosed T1DM.

14. ADVERSE EVENTS & RISKS

There are minimal risks associated with GM. A GM is a self-monitoring of blood sugars via finger-stick that help making treatment decisions about diabetes. There is a small possibility that the measurements may not be accurate. We will consider these factors that affect meter accuracy and the steps to resolve or prevent the problems like test strip problems (Be sure the strips are meant for the meter), keeping the glucose meter and test strips at extreme temperatures (Keep glucose meter at room temperature), improper test strip coding, problems inserting the test strip in the monitor or not enough blood applied to test strip (recommend a generous drop of blood to test strip).

Regarding capillary sampling by finger-stick with a lancet, can carry a small risk of the following: infection, bleeding, pain or local skin irritations including redness, swelling, bruising, itching, scarring or skin discoloration.

15. CONFIDENTIALITY

The study will comply with HIPAA guidelines regarding confidentiality of participant data. Privacy will be assured during the consent and study procedures. During the consent process, potential subjects and their parents will be allowed time to review the informed consent document and ask a member of the research team all their questions regarding the research study. All questionnaires will be labeled with a

study ID. Data, including paper copies of participant data, original signed consent and HIPAA documents, completed questionnaires, and all source documents, will be stored in a medical building with card-coded access inside a locked cabinet. Data stored on the computer will be encrypted and password protected. A separate file will be kept on an encrypted and password protected computer that will contain participant identifiers linking names and contact information to the study for purpose of follow up in this clinical trial. This information will not be entered into the computer system for study data. At completion of study, all participants' identifiable information will be stored at Access Data Management System for a period of 10 years. After 10 years, all information will be destroyed. When papers are published regarding this study and data obtained, only composite data will be used, and each subject's identity will be strictly protected.

Although IRB policies to protect confidentiality of study information will be followed, it is possible that a breach could occur. The following steps will be taken to limit that possibility: 1) Source documents for the study will be stored either in the CHOA HER (Epic) or as hard copies in locked filing cabinets in a locked office at Center for Advanced Pediatrics, 2) All subjects will be assigned a study number and all study records will bear only that number for identification. The key for identifying individual subjects will only be available to study personnel.

16. REFERENCES

1. Shimin Fu, Linjun Li, Shuhua Deng, Liping Zan, Zhiping Liu. Effectiveness of advanced carbohydrate counting in type 1 diabetes mellitus: systematic review and meta-analysis.Sci. Rep.6,37067; doi: 10.1038/srep37067 (2016).
2. Jiansong ao, MSC; Heather R. Gilbertson, PHD, ADVAPD; Robyn Gray, CDE; et al. Improving the Estimation of Mealtime Insulin Dose in Adults with Type 1 Diabetes. The Normal Insulin Demand for Dose Adjustment (NIDDA) study. Diabetes Care 2011. 34(10):2146-2151.
3. American Diabetes Association. 13. Children and adolescents: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S148–S16
4. Laffel LMB, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. J Pediatr 2003;142:409–416
5. Giorgia Tascini, Maria Giulia Berioli, Laura Cerquiglini, Elisa Santi, Giulia Mancini, Francesco Rogari, Giada Toni, Susanna Esposito. Carbohydrate Counting in Children and Adolescents with Type 1 Diabetes. Nutrients. 2018 Jan; 10(1): 109.
6. Leann Olansky MD; Laurence Kennedy MD. Finger-stick Glucose Monitoring. Diabetes Care. 2010; 33(4):948-949.
7. Smart C.E., Aslander-van de Vliet E., Waldron S. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium: Nutritional management in children and adolescents with diabetes. Pediatr. Diabetes. 2009;10:100–117.
8. Shimin Fu, Linjun Li, Shuhua deng, Liping Zan, Zhiping Liu. Effectiveness of advanced carbohydrate counting in Type 1 diabetes mellitus: a systematic review and meta-analysis. Scientific reports, 14 November 2016, Vol.6, pp.37067
9. Bell, K. J., Barclay, A. W., Petocz, P., Colagiuri, S. & Brand-Miller, J. C. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2(2), 133–140 (2014).
10. Sperling, Mark MD. Pediatric Endocrinology. Fourth Edition. 2014. 878-879.
11. Sarafoglou,K; Hoffmann, G; Roth, K. Pediatric Endocrinology and Inborn Errors of Metabolism. Second Edition. 2017. p 310 - 326.

12. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technol Ther. 2019; 21(2):81-85.
13. Alarcon-Casas Wright, L; Hirsch, Irl. Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapautics. 2017; 19(2).
14. Sunghwan Suh, Jae Hyeon Kim. Glycemic Variability: How Do We Measure It and Why Is It Important?. Diabetes Metab J. 2015; 39(4): 273-282.
15. Shapiro, Jenna B; Vesco, Anthony T ; Weil, Lindsey E G ; Evans, Meredyth A ; Hood, Korey K ; Weissberg-Benchell, Jill. Psychometric Properties of the problem Areas in Diabetes: Teen and Parent of Teen Versions. Journal of pediatric psychology, 01 2018, Vol.43(5),pp.561-571
16. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S13–S28
17. Berry, JD, & Jones, W,H. The Parental Stress Scale : initial psychometric evidence. Journal of Social and Personal Relationships 1995; 12 (3):p. 463-472. https://doi.org/10.1177/0265407595123009
18. Oronoz, Beatriz; Alonso-Arbiol, Itziar; et al. A Spanish Adaptation of the Parental Stress Scale Psicothema. 2007; 19 (4): 687 -692. ISSN: 0214-9915

Annex 1: Parental Stress Scale and Scoring.

Parental Stress Scale

The following statements describe feelings and perceptions about the experience of being a parent with a child with new onset type 1 diabetes mellitus. Think of each of the items in terms of how your relationship with your child typically is in the setting of recently diagnosis of diabetes mellitus. Please indicate the degree to which you agree or disagree with the following items by placing the appropriate number in the space provided.

1 = Strongly disagree 2 = Disagree 3 = Undecided 4 = Agree 5 = Strongly agree

1	I am happy in my role as a parent	
2	There is little or nothing I wouldn't do for my child(ren) if it was necessary.	
3	Caring for my child(ren) sometimes takes more time and energy than I have to give.	
4	I sometimes worry whether I am doing enough for my child(ren).	
5	I feel close to my child(ren).	
6	I enjoy spending time with my child(ren).	
7	My child(ren) is an important source of affection for me.	
8	Having child(ren) gives me a more certain and optimistic view for the future.	
9	The major source of stress in my life is my child(ren).	
10	Having child(ren) leaves little time and flexibility in my life.	
11	Having child(ren) has been a financial burden.	
12	. It is difficult to balance different responsibilities because of my child(ren).	
13	The behavior of my child(ren) is often embarrassing or stressful to me.	
14	If I had it to do over again, I might decide not to have child(ren).	
15	I feel overwhelmed by the responsibility of being a parent.	
16	Having child(ren) has meant having too few choices and too little control over my life.	
17	I am satisfied as a parent	
18	I find my child(ren) enjoyable	

Scoring:

To compute the parental stress score, items 1, 2, 5, 6, 7, 8, 17, and 18 should be reverse scored as follows: (1=5) (2=4) (3=3) (4=2) (5=1). The item scores are then summed.

Scoring the tool:

We want a low score to signify a low level of stress, and a high score to signify a high level of stress

- Overall possible scores on the scale range from 18 – 90.
- The higher the score , the higher the measured level of Parental stress

Use a simple table to show the before and after results to evidence whether an intervention has had a positive effect.

- Comparison of individuals before / after or longitudinal overall Parental Stress Scale scores.
- The comparison of before and after mean average scores for groups (parents/care givers accessing the particular intervention/group sessions, service or provision).

Annex 2: Spanish version of Parental Stress Scale and Scoring.

Escala de Estres Parental

Las siguientes oraciones describen sentimients y percepciones acerca de como un padre/madre/cuidador se siente cuidando a un nino que ha sido diagnosticado con diabetes mellitus recientemente. Responder cada pregunta pensando en como es la relacion entre su nino(a) con usted desde el diagnostico de diabetes mellitus.

Indicar el grado de acuerdo o desacuerdo en cada una de las siguientes preguntas y coloque el numero apropiado en el espacio correspondiente.

1 = Totalmente en desacuerdo
2 = Desacuerdo
3 = Indeciso
4 = De acuerdo
5 = Totalmente de acuerdo

1	Me siento feliz en mi papel como padre/madre	
2	No hay nada o casi nada que no haria por mi hijo/a si fuera necesario	
3	Atender a mi hijo/a a veces me quita mas tiempo y energia de la que tengo.	
4	A veces me preocupa el hecho de si estoy hacienda lo suficiente por mi hijo/a	
5	Me siento muy cercano/a a mi hijo/a	
6	Disfruto pasando tiempo con mi hijo/a	
7	Mi hijo/a es una fuente importante de afecto para mi	
8	Tener un hijo/a me da una vision mas certera y optimista para el future	
9	La mayor fuente de estres en mi vida es mi hijo/a	
10	Tener un hijo/a deja poco tiempo y flexibilidad en mi vida.	
11	Tener un hijo/a ha supuesto una carga financiera	
12	Me resulta dificil equilibrar diferentes responsabilidades debido a mi hijo/a	
13	El comportamiento de mi hijo/a menudo me resulta incomodo o estresante	
14	Si tuviera que hacerlo de Nuevo, podria decider no tener un hijo/a	
15	Me siento abrumado/a por la responsabilidad de ser padre/madre	
16	Me siento satisfecho/a como padre/madre	
17	Disfruto de mi hijo/a	

Scoring:

Participants will be asked to rate each one on a 1-to-5 Likert-type response scale ranging from 1 (strongly disagree [*totalmente en desacuerdo*]) to 5 (strongly agree [*totalmente de acuerdo*]). The items appeared in the same order as in the English-language PSS (except for the eliminated item 16 in the English version.). The total score was obtained by summing up the value for each item (reversed items are 1, 2, 5, 6, 7, 8, 16, and 17). A higher score indicates a higher level of parental stress.