HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: A Very Low Carbohydrate Diet as an Adjunctive Therapy for Youth Type 1 Diabetes

Principal Investigator: Laura Nally, MD

Version 4 Date: November 18, 2021

Clinicaltrials.gov Registration #: NCT04082884

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** This prospective, open-label pilot/feasibility study of youth with T1D is to evaluate glycemic and metabolic changes taking place with a very low carbohydrate diet.
2.
3. **Probable Duration of Project:** The expected duration of the project is 5 years, including all follow-up and data analysis activities.

4. **Background:** As recently reported by the Type 1 Diabetes Exchange (T1DX) Registry, adolescents with type 1 diabetes (T1D) was the age group that had the highest hemoglobin A1c (A1c) levels compared to older participants; young adults aged 10-25 years were a close second (1). While the American Diabetes Association (ADA) recommends youth target A1c of <7.5% and adults <7%, only 17% of youth and 21% of young adults in the T1DX achieved these targets despite increased penetrance of diabetes technologies into clinical care (1, 2). These data suggest a need for novel approaches to improve glycemic control in adolescents and young adults with T1D.

   Even for compliant youth with T1D, postprandial hyperglycemia continues to pose a challenge for many reasons, including, delayed insulin absorption and action compared to absorption of glucose from the gastrointestinal tract and dysregulated glucagon secretion after mixed meals (3). Moreover, postprandial glycemic changes can differ substantially depending on the macronutrient composition of the meal. Specifically, meals with reduced carbohydrate but increased fat and protein content will lessen immediate postprandial hyperglycemia (4). For many, being able to avoid carbohydrates and adhere to a very low carbohydrate diet may be easier than administering varying amounts of insulin for variable amounts of carbohydrate intake. Although standard treatment of T!D recommends varying the pre-meal dose of rapid-acting insulin depending on the patient's insulin to carbohydrate ratio, studies have shown that inaccurate carbohydrate counting happens frequently and contributes to increased glycemic variability (5).

   Data from the Diabetes Control and Complications Trial (DCCT) demonstrated that lowering the A1c by intensive insulin management to near-normal glycemic levels decreases the risk of complications related to diabetes (6). However, intensive management in the DCCT was accompanied by marked increases in severe hypoglycemia and more recent data have implicated increased insulin doses as risk factors for cardiovascular disease in T1D (7). One approach to achieve targeted glycemic control with less insulin exposure is through the use of a very low carbohydrate diet (VLCD), defined as limiting carbohydrate intake to 50 grams per day or less (8). In adults with T1D, these diets have been shown to achieve exceptional glycemic control with physiologically normal A1c values with lower total daily insulin doses due to decreased mealtime insulin for low amounts of carbohydrate intake (9, 10).

   Importantly, VLCDs have not been formally studied in adolescents and young adults with T1D. Observational data on children using a VLCD are also conflicting. A small case series of 6 children with T1D on a low carbohydrate diet showed deficits in anthropomorphic measurements and elevated lipids, though in some cases a caloric deficit was also reported (11). Conversely, a recent observational study of 131 children with T1D on a VLCD reported no significant change in height percentile or SDS after initiating the diet (12). Prior studies have explored use of low carbohydrate diets in T1D, but none have specifically monitored for ketosis. In those studies, it is likely that the lack of carbohydrate intake led to lower insulin needs, thus increasing lipolysis and ketogenesis, and levels of ketosis while on this type of diet require further study (13).

Since rigorous studies implementing a VLCD in youth with T1D remain to be done, the present pilot study is being undertaken to evaluate the glycemic and metabolic changes that accompany initiation of a very low carbohydrate diet in adolescents and young adults with T1D who are receiving insulin pump therapy. Specifically, we will measure changes in plasma glucagon, *β*-hydroxybutyrate, and free fatty acid (FFA) levels, as well as changes in basal hepatic glucose production, glycerol turnover, lipid oxidation and plasma glucagon responses to arginine infusions. Continuous glucose monitoring will be used to evaluate changes in plasma glucose responses to meals before and after initiation of the VLCD. Insulin pump downloads will be employed to assess changes in basal and bolus insulin doses.

Aims: To examine changes in sensor glucose levels, basal and bolus insulin doses, and FFA, glucagon, and *β*-hydroxybutyrate levels following implementation of a VLCD. Sensor-derived time glucose ranges will serve as a surrogate marker of hemoglobin A1c given the short duration of the study. We will also be assessing safety measures of the diet, including daily fasting ketone levels. Hypothesis: We hypothesize that use of a VLCD with strict monitoring of ketosis will reduce glycemic variability and increase time in target range, defined as 70-180 mg/dL by reducing the time in the hyperglycemic (>180 mg/dL) and hypoglycemic ranges (<70 mg/dL). Decreased carbohydrate intake will lead to less postprandial hyperglycemia. Lower insulin doses for meals and snacks as a result of decreased carbohydrate intake will lessen postprandial hypoglycemia as well.

Further, we will also measure changes in glucose and glycerol metabolic fluxes using stable isotopes and indirect calorimetry to measure rates of fat oxidation before and after 2 weeks of a VLCD. Arginine infusion will used to assess changes in plasma glucagon responses with the VLCD. Hypothesis: Glucose and glycerol turnover will be increased in those with T1D on a very low carbohydrate diet. Lipid oxidation will also be increased. We further hypothesize that the arginine-stimulated glucagon response will be increased while on the VLCD will, in turn, decrease the risk of late post-meal hypoglycemia during the VLCD.

Research Plan: This prospective feasibility study of 10 youth (ages 13 – 25) with T1D will evaluate glycemic and metabolic changes after 2 weeks of a high protein VLCD compared to 2 weeks on a standard carbohydrate diet (see Table 1). The study will take place in 2 parts. Part 1 will only involve the high protein VLCD, but part 2 will involve high protein VLCD and high fat VLCD's.

Table 1. Types of study diets and macronutrient content in each planned diet.

Type of Diet	Carbohydrates	Protein	Fat
Standard Carbohydrate	25%+	Not specified	Not specified
High Protein VLCD	11%	54%	35%
High Fat VLCD	11%	23%	66%

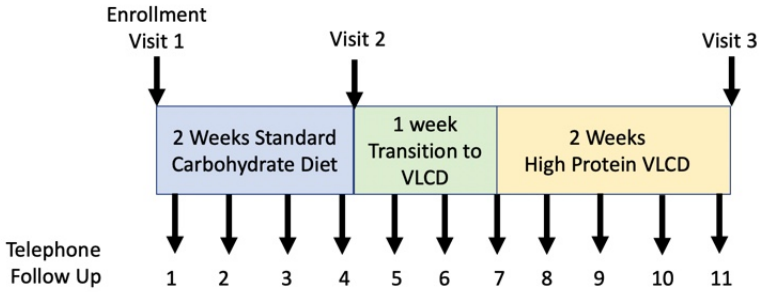
Part 1: First, to evaluate the feasibility of following a high protein VLCD, participants will follow a standard carbohydrate diet for 2 weeks, followed by a 1 week transition to a VLCD, and then follow the a high protein VLCD for 2 weeks. The study will consist of 3 in person or virtual visits which will take place over ~5 weeks. All participants will be initially studied for 2 weeks while ingesting a standard diet recommended by the American Diabetes Association, followed by a 1-week transition to a VLCD, and followed by 2 weeks on the high protein VLCD. During the first (baseline) period fasting *β*-hydroxybutyrate levels will be measured 2-3 times per week. During the VLCD study periods, fasting *β*-hydroxybutyrate levels will be measured daily in the morning using a blood ketone meter; insulin doses will be collected using insulin pump downloads and continuous glucose monitoring (CGM) profiles will be used to assess glycemic excursions on each diet, as

well as the time in hypo-, eu- and hyperglycemic ranges. Part 1 of the study is anticipated to be complete by December 31, 2022.

5. **Participants**: This study will enroll 10-20 participants (ages 13 to 25) with T1D. At least 4 adults over the age of 18 will be enrolled. Ten youth will be involved in Part 1, which evaluates feasibility of the diet. If those youth would like to continue to Part 2 of the study they may continue, or they will be replaced by new participants. To be eligible for inclusion, the participant must have T1D for at least 1 year, have an A1c between 6.5% to 10.0% inclusive, and BMI of at least 19 kg/m2 (or 5th percentile for those under age 18) and be willing to wear a CGM, which is the currently recommended standard of care for children with type 1 diabetes and is FDA approved for use above age 2 years. They must also be willing to adhere to a VLCD, measure β-hydroxybutyrate levels daily and to keep a detailed food diary. Participants who are unable to wear a CGM, monitor their diabetes control or maintain the VLCD will be replaced.

   Study visits: Participants will be recruited from Yale Pediatric Diabetes Center and Yale Diabetes Center clinics, as well as through social media. All participants will undergo pre-screening of their electronic medical record (or faxed medical record from their pediatric endocrinologist or endocrinologist) to evaluate study eligibility by review of medical history, as well as prior physical exams and laboratory tests. No blood will be collected in part 1 of the study.

   Figure 1. Timeline of visits and telephone follow ups for the duration of the study. Visits and calls may be modified depending on patient availability and academic schedule. Part 1 of the study will involve in-person or virtual visits (Facetime, Video Doximity Calls, Zoom, or Skype) and telephone study visits. Part 2 of the study will involve in-person visits.



Screening & Enrollment Visit 1: Screening will be conducted by invitation to potentially eligible subjects. For the first part of the study, the study will be explained and telephone or e-consent will be obtain prior to conducting any study procedures. Participants will 1) meet in person or 2)use telephone to discuss the study or 3) Skype, Zoom, FaceTime or Doximity Dialer enabling video calls. Scales will be provided for all participants.

Consent: Consent will be transitioned to an online/electronic format using the YSM version of REDCap if consent is not obtained in person.

- Two copies of the consent form will be sent to subjects by mail, fax, or e-mail, prior to the consenting phone call so that subjects have time to review the consent prior to signing it and so

that subjects have a physical copy in hand to follow along and ask questions during the consenting phone call/virtual visit.

- The consent will be signed and dated by the participant and returned via a self-addressed envelope or faxed to the research team. It will be signed and dated by the person obtaining consent upon receipt.
- Once the consent is signed by the research team member, it will be filed in the subject's research record.
- A note to file to document the consenting process took place over the phone, which explains the difference in dates, will be completed and stored with the signed consent forms.

After consent has been obtained, participants will review their diabetes history and answer demographic questions. At this and all other study visits, participants will meet (virtually or in person for part 1) with a diabetes care provider (i.e., a physician, nurse practitioner, or physician assistant) who will carry out a comprehensive review of diabetes management and review blood glucose and ketone records. Participants will be asked to rate their puberty status in lieu of a physical exam for puberty. A validated system for self-assessment of puberty status that has been used by pediatricians will be used for this study. Women of childbearing age will have a urine pregnancy test performed at the time of the screening/enrollment visit and the need for contraception for the entire duration of the study will be discussed. If pregnancy testing cannot be performed in-person, a pregnancy test will be mailed to the participant an we will ask them to securely send a photo of the results to the study team. The treatment regimen will be adjusted as clinically indicated. Individuals will be asked to wear a continuous glucose monitor (CGM) during the 2-week standard carbohydrate and 2-week VLCD assessment period. A CGM will be provided if the individual does not have one that they use as a part of routine care. Insulin pumps and CGMs will be downloaded to assess prior glycemic control.

Baseline data obtained at the enrollment visit will include:

- Demographic characteristics, including family income, highest parental education attained, and number of individuals in the home.
- Anthropometric measures will be reviewed from the most recent clinic visit, including height, weight, BMI, vital signs). Participants will self-identify their tanner stages based on gender-specific norms.
- Current diabetes care practices (frequency of self-monitored blood glucose (SMBG), insulin dosing, review of blood glucose values)
- Medical History: duration of diabetes, comorbidities, past medical history, social history, family history, medications, and allergies.
- Additional diabetes history including current/past use of CGM, insulin pump, and other modes of diabetes technology.
- Frequency of missed school days and Emergency Department visits due to decompensated diabetes (i.e., hyperglycemia, ketosis and DKA) over the past 6 months
- Questionnaires will be administered, including:
    a. Diabetes Treatment Satisfaction Questionnaire (DTSQ), which includes eight items, six of which form a scale (scored 0-36) in which higher scores indicate greater treatment satisfaction (Bradley, 1994).
    b. Nutrition Knowledge Survey (NKS) which collects information on healthful eating, carbohydrate counting, blood glucose response to foods, and nutrition label reading. Higher NKS scores reflect greater nutrition knowledge (score range is 0–100%) (Rovner 2012).
    c. Diabetes Distress Scale (DDS) is a 17-item scale that captures diabetes distress in 4 different areas, including emotional burden, regimen distress, interpersonal distress, and physician distress (Polonsky 2005).

All participants will receive dietary instruction to review the dietary requirements of the study. A handout with examples of the type of diet required will be provided to each participant at the time of or prior to consent. Participants will provide a 3-day dietary history at the enrollment visit to assess current caloric intake. Each subject will be instructed on how to keep a food diary. Participants and/or parents will be asked to take photos of all food consumed to aid in dietary recall. After the enrollment visit, participants will be contacted to assess adherence to the diet and adjust insulin doses 3 times per week (see Table 1). During these telephone follow up calls, food diary will be reviewed, photos of meals will be reviewed, and pump and CGM data will be uploaded and reviewed. Participants will receive a link in their email to fill out the 3 surveys using Yale Qualtrix.

Visit 2: After 2 weeks on the standard carbohydrate diet, insulin pump and CGM data will be uploaded (Tidepool, Dexcom, Medtrnoic, Omnipod or Tandem site, depending on the insulin pump being used) and reviewed. Dose adjustments will be made as clinically indicated. Participants will receive a link in their email to fill out the 3 surveys using Qualtrix.

The dietician will look at each individuals macronutrient intake during the standard carbohydrate portion of the study. Based on this information, we will instruct them to eat a certain amount of carbohydrates each day. If they eat more than 200 grams per day of carbohydrates during the standard diet weeks, they will be instructed to eat 100-150 grams of carbohydrates per day during the transition week. If they eat less than 200 grams per day of carbohydrates during the standard diet weeks, we will instruct them to eat 75-125 grams of carbohydrates per day during the transition week. Most people with diabetes know how to carbohydrate count, however we will review carbohydrate counting at the time of the transition. Carbohydrate counting will be taught using the "Choose Your Foods: Food Lists for Diabetes" written by the American Diabetes Association and the American Nutrition of Dietetics.

For the VLCD portion of the study, participants will be given an isocaloric diet with a goal carbohydrate intake of less than 20% carbohydrates per day (~100 grams per day) for adolescents and less than ~50 grams per day for adults at least 18 years of age. Guidelines will be provided for meals. Participants will also receive training on the treatment of hypoglycemia and be instructed to call the study team immediately in the case of severe hypoglycemia.

Visit 3: After at least 2 weeks on each of the very low carbohydrate study diets, participants will meet virtually with study staff to review isulin pump and CGM data. Insulin pump and CGM data will be uploaded (Tidepool, Dexcom, Medtrnoic, Omnipod or Tandem site, depending on the insulin pump being used) and reviewed virtually, as is commonly done in clinical practice. Dose adjustments will be made as clinically indicated. Participants will receive a link in their email to fill out the 3 surveys using Qualtrix.

Part 2: In the second part of the study, participants will once again begin on a standard carbohydrate diet for 2 weeks and then be randomized to either a high fat VLCD or high protein VLCD. They will transition over a 1 week period to one of these 2 diets, and then will follow the diet for an additional 2 weeks. As in the first part of the study, they will have 3 visits over 5 weeks. At the end of each 2-week period, we will evaluate glucose and glycerol fluxes and fat oxidation in the Hospital Research Unit (HRU) or Church Street Research Unit (CSRU) as well as plasma glucagon and glucose excursions after an arginine infusion. This study will be completed after completion of part 1. The total duration of the study is anticipated to be 2 years, anticipated end date December 31, 2023.

Screening & Enrollment Visit: Screening will be conducted by invitation to potentially eligible subjects. Written informed consent will be obtained prior to conducting any study-related procedures. After consent has been obtained, subjects will review their diabetes history and answer demographic questions. At this and all other

study visits, participants will meet with a diabetes care provider (i.e., a physician, nurse practitioner, or physician assistant) who will carry out a comprehensive review of diabetes management and review blood glucose and ketone records. The treatment regimen will be adjusted as clinically indicated. Individuals will be asked to wear a continuous glucose monitor (CGM) during the 2-week standard carbohydrate and 2-week VLCD assessment periods. A CGM will be provided if the individual does not have one that they use as a part of routine care. Insulin pumps and CGMs will be downloaded to assess prior glycemic control.

Women will have a urine pregnancy test performed at the time of the screening/enrollment visit and the need for contraception for the entire duration of the study will be discussed.

Baseline demographic information will be obtained, including:

- Demographic characteristics, including family income, highest parental education attained, and number of individuals in the home.
- Anthropometric measures will be measured, including height, weight, BMI, and vital signs.
- Participants will undergo a physical exam, including tanner staging.
- Point of care HbA1c, obtained via fingerstick and measured by a Seimens DCA Vantage device, will be determined unless an A1c was measured in clinic within the past 30 days.
- Current diabetes care practices (frequency of self-monitored blood glucose (SMBG), insulin dosing, review of blood glucose values)
- Medical History: duration of diabetes, comorbidities, past medical history, social history, family history, medications, and allergies.
- Additional diabetes history including current/past use of CGM, insulin pump, and other modes of diabetes technology.
- Frequency of missed school days and Emergency Department visits due to decompensated diabetes (i.e., hyperglycemia, ketosis and DKA) over the past 6 months
- Baseline laboratory assessment if it has not been done in the past year, as a part of standard of care (comprehensive metabolic panel with electrolytes, lipid panel, urine microalbumin).
- Questionnaires will be administered, including:
    a. Diabetes Treatment Satisfaction Questionnaire (DTSQ), which includes eight items, six of which form a scale (scored 0-36) in which higher scores indicate greater treatment satisfaction (Bradley, 1994).
    b. Nutrition Knowledge Survey (NKS) which collects information on healthful eating, carbohydrate counting, blood glucose response to foods, and nutrition label reading. Higher NKS scores reflect greater nutrition knowledge (score range is 0–100%) (Rovner 2012).
    c. Diabetes Distress Scale (DDS) is a 17-item scale that captures diabetes distress in 4 different areas, including emotional burden, regimen distress, interpersonal distress, and physician distress (Polonsky 2005).

All participants will receive dietary instruction to review the dietary requirements of the study. A handout with 2 examples of the type of diet required will be provided to each participant at the time of or prior to consent. Participants will provide a 3-day dietary history at the enrollment visit to assess current caloric intake. Each subject will be instructed on how to keep a food diary. Participants and/or parents will be asked to take photos of all food consumed to aid in dietary recall. After the enrollment visit, participants will be contacted to assess adherence to the diet and adjust insulin doses 3 times per week (see Table 1). During these telephone follow up calls, food diary will be reviewed, photos of meals will be reviewed, and pump and CGM data will be uploaded and reviewed.

Prior to the HRU/CSRU admission, we will recommend a standard diet be given and no food be eaten after 9pm (except for in cases of hypoglycemia). Participants will be advised to limit exercise in the 3 days prior to study to limit acute effects of recent exercise on insulin sensitivity.

Visit 2: After at least 2 weeks on the standard carbohydrate diet, participants will be admitted to the HRU or CSRU for the equilibration portion of the study and arginine stimulation test. The subject may arrive at 7:30 a.m. the morning of the study. The study nurse will do a nursing assessment, including measuring the subject's temperature, blood pressure, and pulse. A urine pregnancy test will be performed and we will discuss the need for contraception during the VLCD portion of the study. Two indwelling catheters will be placed, one into an antecubital vein for infusion of test substances and a second catheter into a contralateral vein for blood sampling.

The study will begin with a ~150 minute equilibration period during which we will aim to keep glucose levels stable, followed by an arginine stimulation test. Blood draws for measurements of glucose and glycerol enrichment are listed in tables 2, 3, and 4.

Subjects will be asked permission to allow the serum and information collected during this research study to be used for future research purposes. The serum samples may be used by our research group to run additional assays related to the pathophysiology of diabetes.

- *Fasting laboratory assessment:* Upon arrival, participants will have blood tests performed, including *β*-hydroxybutyrate, free fatty acids (FFA), glucagon, comprehensive metabolic panel, magnesium level.

- *Non-radioactive*, *Stable Isotope Tracer Infusions* will be employed to assess rates of glucose and glycerol metabolism at the end of the ~150-minute baseline equilibration period. From -150 to 0 min, 4.5 mg/kg of 6,6-$^{2}H_2$-glucose (99% enriched; Cambridge Isotope Laboratories, Andover MA) will be followed by a continuous infusion at 0.06 mg/kg/min. $^{2}H_5$- glycerol will be infused at 1.6 µmol/kg followed by a constant infusion of 0.11 µmol/kg/min to assess glycerol turnover. During the basal turnover period, a variable rate insulin infusion may be utilized to maintain plasma glucose between ~80-120 mg/dL. As results from prior participants become available, infusions of the isotopes may be adjusted in subsequent participants to ensure enrichment is not too low for measurement.

- *Metabolite Collection:* Samples for measurements of glucose and glycerol enrichment, as well as hormones and substrates, will be obtained every ~15-30 minutes of the baseline equilibration phase (see Table 2). Additional blood samples at baseline will be collected and used to derive additional metabolic risk markers of timely interest; specific uses are to be determined but will only be conducted after corresponding future protocol approvals. Biomarkers collected as part of this research will be stored by the YCCI core lab services.

- *Measures of Oxidation:* Indirect calorimetry will be utilized at each HRU/CSRU visit to evaluate rates of glucose and fat oxidation.

- *Arginine Stimulation Test (AST)*: An AST will be conducted as a gold-standard assessment of islet hormone secretion, specifically, that of glucagon through stimulation of α cells. At time 0, arginine will be administered (5g of 10% solution) over ~ 1 minute. We will measure stimulated glucagon, glucose, ketone, and c-peptide levels after arginine stimulation. Blood glucose samples will be taken

at baseline and every ~15 min for 60 minutes, centrifuged, and measured at bedside with an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH).

- *Questionnaires:* Participants will be asked to complete Diabetes Treatment Satisfaction Questionnaire, Nutrition Knowledge Survey, and Diabetes Distress Scale. These questionnaires should take no more than 10-15 minutes total to complete.

Upon completion of the AST, participants will meet with study staff to review the requirements of the transition week and VLCD portion of the study. The dietician will look at each individuals macronutrient intake during the standard carbohydrate portion of the study. Based on this information, we will instruct them to eat a certain amount of carbohydrates each day. If they eat more than 200 grams per day of carbohydrates during the standard diet weeks, they will be instructed to eat 100-150 grams of carbohydrates per day during the transition week. If they eat less than 200 grams per day of carbohydrates during the standard diet weeks, we will instruct them to eat 75-125 grams of carbohydrates per day during the transition week. Most people with diabetes know how to carbohydrate count, however we will review carbohydrate counting at the time of the transition. Carbohydrate counting will be taught using the "Choose Your Foods: Food Lists for Diabetes" written by the American Diabetes Association and the American Nutrition of Dietetics.

For the VLCD portion of the study, participants will be given an isocaloric diet with a goal carbohydrate intake of less than 20% carbohydrates per day (~100 grams per day) for adolescents and less than ~50 grams per day for adults at least 18 years of age. Guidelines will be provided for meals. Participants will also receive training on the treatment of hypoglycemia and be instructed to call the study team immediately in the case of severe hypoglycemia.

Visit 3: After at least 2 weeks on the very low carbohydrate study diet, participants will be admitted to the HRU/CSRU and repeat the same protocol listed in Visit 2.

Table 1. Planned study interventions for part 2 of the study.

Measurement	Wk 0	Phone wk 0.5	Phone wk 1	Phone wk 1.5	Visit end wk 2	Transition to VLCD wk 2-3	Phone wk 3	Phone wk 3.5	Phone wk 4	Phone wk 4.5	Visit end wk 5
Dietary Recall, assessment for symptoms related to VLCD	X	X	X	X	X	X	X	X	X	X	X
Diabetes management review, dose adjustments as needed, CGM data analysis	X	X	X	X	X	X	X	X	X	X	X
Baseline laboratory assessment	X										

Fasting laboratory assessment					X						X
Stable isotope study of glucose and glycerol metabolism, indirect calorimetry, arginine stimulation test					X						X
Diabetes Treatment Satisfaction Questionnaire	X				X						X
Diabetes Treatment Satisfaction Questionnaire (Change)											X
Nutrition Knowledge Questionnaire	X				X						X
Diabetes Distress Scale	X				X						X

Table 2. Planned blood tests during the baseline glucose and glycerol turnover study.

Time (minutes)	***-150***	***-120***	***-90***	***-60***	***-30 steady state***	***-15 steady state***
Glycerol (2mL)	*X*	*X*	*X*	*X*	*X*	*X*
Glucose (0.5 mL)	*X*	*X*	*X*	*X*	*X*	*X*

Table 3. Planned blood tests during arginine stimulation testing. Time 0 represents time of Arginine infusion.

Time (minutes)	***-15***	***0***	***5***	***15***	***30***	***45***	***60***
BOHB (0.3 - 1mL vs use meter)	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Glucose (0.5mL)	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Glucagon (2mL)	*X*	*X*	*X*	*X*	*X*	*X*	*X*
C-peptide (3mL)		*X*			*X*		*X*

Storage (3mL)	*X*	*X*	*X*	*X*	*X*	*X*	*X*

Table 4. Blood volume collected during each HRU visit.

Weight (kg) at Blood Draw	Equilibration	Arginine stimulation Test	Fasting laboratory assessment	Storage (Serum)	Total Blood Volume Collected (mL)	Total Blood Volume Collected (mL/kg)
40 to 42	36 mL	51.5 mL	11 mL	24 mL	122.5	~3
43 to 65	36 mL	51.5 mL	11 mL	24 mL	122.5	1.9-2.8
>65	36 mL	51.5 mL	11 mL	24 mL	122.5	<1.9

6. Genetic Testing N/A ☒

7. **Subject Population:**

Part 1: 10 participants ages 13 to 25 years of age with a clinical diagnosis of T1D for at least 1 year will be enrolled for 5-6 weeks for part 1 of the study. Participants who reach the age of majority during the study will be re-consented using the adult consent form.

Part 2: 10 participants ages 13 to 25 years of age with a clinical diagnosis of T1D for at least 1 year will be enrolled for 5-6 weeks for part 1 of the study. Participants who reach the age of majority during the study will be re-consented using the adult consent form.

8. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☒Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

Rationale for studying adolescents: Effective glycemic control is needed to prevent future micro and macrovascular complications of T1D. Thus, it is critical to investigate ways to improve control in adolescents (both male and female), the population with the poorest glycemic control across all age ranges. The proposed study will employ a novel method that may limit acute complications of T1D, as well as improve overall glycemic control. Such studies can only be carried out in adolescents, due to the unique characteristics of this cohort.

9. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

<u>Inclusion Criteria</u>:

Ages 13-25 years old

BMI > 19kg/m^2 for individuals at least 18 years old or greater than the 5%ile for those under age 18

Participants 18 years of age must be able to read and provide written consent

Participants under 18 years of age must be able to read and provide written assent

Participants are managed using an insulin pump or injections
Participant has or is willing to wear a CGM for the duration of the study as described above
Participant is willing to complete diet logging procedures stated above

Exclusion Criteria:

A1c < 6.5% or > 10%
Recent history of more than 1 of diabetic ketoacidosis (DKA) in the past 6 months
Treatment with glucose-lowering drugs other than insulin
Unstable psychiatric disorders, including eating disorders (DSM-V criteria)
Weight loss medications within the last 6 months
Females who are pregnant, lactating or planning to become pregnant in the next 6 months.
Another medical condition that precludes participation in the study.

10. How will **eligibility** be determined, and by whom? Eligibility will be determined by the PI or a co-investigator, and/or study team member who will verify that the parent/caregiver meets inclusion/exclusion criteria.

11. **Risks:**

- Risks of Very Low Carbohydrate Diet: Previous studies have suggested that switching to a very low carbohydrate diet can cause symptoms including nausea, vomiting, abdominal pain, constipation, fatigue, and lightheadedness. These symptoms will be screened for at follow up visits throughout the study (see Table 1).
- Hypoglycemia/Hyperglycemia: Participants in the study will be at risk of hypoglycemia and hyperglycemia. For this reason, during the HRU/CSRU admission, blood glucose levels are measured frequently throughout the study by a reliable device (YSI 2300) so that if needed, dextrose infusion can be utilized to prevent hypoglycemia. The study procedures may result in elevated or low glucose values. At the end of each visit, the participant will receive guidance for glucose monitoring, food intake, and insulin dosing as needed. During the study, dose adjustments will be made according to standard of care to prevent hypoglycemia and hyperglycemia.
- Stable isotopes: Despite the theoretical risk of infection with infusion of stable isotopes, our team has been using isotopes during studies for 15 years in children and adolescents and have not experienced any adverse events.
- Risk of Indirect Calorimetry: The air under the hood may become warm and stuffy, which some subjects find uncomfortable. Rarely, subjects may feel nauseated and/or claustrophobic while under the hood.
- Risk of indwelling catheter: There are potential complications associated with indwelling catheters, including hematomas, discomfort, and rarely infection, thrombophlebitis, or bleeding at the catheter insertion site.
- Anemia: The risk of anemia exists in studies with frequent blood draws. In our many years of performing studies we have not known any participants to experience this complication. The volume of blood draw at each visit will vary depending on the participant's age and weight. However, for children <18 years the maximum blood volume will not exceed 5 cc/kg body weight over a 1-month period. The exact blood volumes collected may vary according to local IRB regulations. The maximum blood volume collected from adults >18 years will not exceed 250cc over a 1-month period.
- Risk of loss of confidentiality: As in any study, there is the potential for loss of confidentiality. Female subjects of childbearing potential will require urine pregnancy testing prior to enrollment in the protocol, and results of this testing have potential to result in loss of confidentiality.
- Risk of glycemic deterioration: It is possible that changing dietary requirements or insulin doses may result in glycemic deterioration. Likewise, adolescents may have glycemic deterioration due to non-compliance.

- Risk of CGM: Participants have the option of using FDA approved CGM as part of clinical care in our clinics. There is a low risk of developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, mild bleeding, and or bruising may occur at the insertion site. Subjects may develop localized reactions to adhesive used to secure the sensor.
- Risk of study questionnaires: Participants may experience some distress when discussing factors important to diabetes, diabetes management, and psychosocial stressors
  - Arginine Stimulation Test: Intravenous infusion of glucose may cause venous irritation (phlebitis) or less commonly infiltration of the surrounding tissues, both which may be discomforting. Intravenously administered arginine may cause a transient metallic taste in the mouth, and less often a transient sensation of warmth or nausea; allergy is rare.

Minimizing Risks:

- Risks of Very Low Carbohydrate Diet: In order to minimize the symptoms associated with transitioning to a low carbohydrate diet abruptly, participants will be slowly transitioned over 1 week to help them acclimate and avoid unwanted symptoms.
- Hypoglycemia/Hyperglycemia: Participants will be contacted frequently during the course of the study. Blood draws will be done frequently during the HRU or CSRU admission to minimize hypoglycemia and hyperglycemia. Intravenous glucose will be available in case hypoglycemia occurs. All infusates containing insulin are prepared under a filtration cabinet (Laminated HLDA filter) by a qualified member of the research team using sterile disposable materials.
- Participants will be encouraged to monitor closely for signs of glycemic deterioration and will be able to contact our diabetes staff at any time if concerns arise.
- At the end of each visit, the participant will receive guidance for glucose monitoring, food intake, and insulin dosing as needed.
- During the study, insulin doses will be adjusted regularly (2-3 times per week as needed) to prevent hypoglycemia. Participants will use a real-time CGM that will provide alerts at the time of hypoglycemia and allow for early detection of hypoglycemia as well. Participants will be trained on treatment of hypoglycemia and to contact the study team immediately in any case of severe hypoglycemia.
- If any subject has 2 episodes of severe hypoglycemia, they will be transitioned to a regular diet after the 2nd episode of severe hypoglycemia.
- Stable isotopes: Isotopes will be carefully monitored, administered and will be prepared in the investigational pharmacy to ensure proper technique. As noted in previous protocols using this stable isotope, the pyrogenicity and sterility of the isotopes are documented by Cambridge Isotopes before they are shipped to YNHH IDS. Methods to Ensure Compound Sterility and Pyrogenicity: All stable isotopes are purchased from Cambridge Isotopes (Boston, MA) and are sent to us sterile and pyrogen-free as specified in the certification form of analysis that is attached to each order. In addition, all infusates containing the isotope that will be used in the study are prepared by the Yale Investigational Drug Service (IDS) by using specific filters (0.22µ). Furthermore, we also use microfilters at the end of each syringe as another safety precaution. All stable isotopes are stored by the Yale IDS and are sent to the YCCI the morning of the study.
- Risk of Indirect Calorimetry: Potential feelings related to wearing the "hood" will be discussed with participants ahead of time, if participants become uncomfortable while wearing the hood it will be removed.
- Arginine Stimulation Test: Intravenously administered arginine may cause a transient metallic taste in the mouth, and less often a transient sensation of warmth or nausea; allergy is rare.
- Risk of indwelling catheter: IV insertion will be performed by trained research nurses on the HRU/CSRU. Trained nurses will use aseptic technique to insert the IV catheters. We will minimize the risk of pain by

offering an option of topical anesthetic to the patient prior to IV insertion. Participants will be advised to contact the study team immediately if they become aware of a late adverse effect.

- Anemia: Samples will be obtained with the minimum necessary blood volume. The point of care YSI glucose determinations require only 0.3ml of blood. We will ensure that blood volume obtained does not exceed a maximum of 5mL/kg in pediatric participants and 250 mL in adult participants.
- Risk of loss of confidentiality: All study staff are HIPPA certified. Participant names and study records will be kept confidential. The IRB may inspect study records at any given time. All efforts will be made to maintain the participants' privacy. Each participant will be assigned a study ID code and data will be linked by this study ID rather than by names, initials, social security numbers, or other personal identifiers. Paper documents will be stored in locked areas accessible only to authorized staff. All electronic data files will be protected by passwords limiting access to the files only to those with a legitimate responsibility for data entry or management. This ensures that, in the unlikely event that any primary data sources from this study are lost or misplaced, it will not be possible to identify the study participant. Copies of informed consent/assent forms and families' contact information will be stored separately from the other study data, which will not contain names or other identifying information. Identifiable study information will be maintained for 10 years after the research is complete. After that time, it will be destroyed or de-identified. The principal investigator will keep a link that identifies subjects to coded information, but this link will be kept secure and available only to the PI or selected members of the research team.
- Risk of CGM: Risks of glucose sensor insertion will be minimized because participants will be instructed to cleanse skin aseptically prior to insertion. Participants will receive training on sensor use if they have not used the sensor previously.
- Risk of study questionnaires: Study staff and social work will be contacted to support families as needed.

12. Data and Safety Monitoring Plan:

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? **Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects**

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? **Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects**

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. Greater than minimal

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require

modification/amendment, or close to enrollment. Either the principal investigator, the IRB or [*enter the names of other oversight bodies that have this authority, e.g.,* Yale Cancer Center Data and Safety Monitoring Committee (DSMC)] have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with the arginine infusion as minimal risks.
2. Given the now established safety and validity of the current isotope infusions and arginine stimulation tests in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (*Insert Investigator Name*) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;

2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring

Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X National Institutes of Health

The principal investigator (*Laura Nally*) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: **N/A**

13. **Statistical Considerations:**

- For part 1 and part 2, descriptive statistics of sensor glucose values, including average glucose, standard deviation, and coefficient of variation
- For part 1 and part 2 of the study, paired t-tests will be used to evaluate differences between the two dietary interventions with respect to
    - Percent time in range for sensor glucose values (70-180mg/dl)
    - Sensor-derived average glucose
    - % Time severe hypoglycemia (<55 mg/dL)
    - % Time hypoglycemia (<70mg/dL)
    - % Time hyperglycemia (>180mg/dl)
    - % Time severe hyperglycemia (>250 mg/dL)
- With respect to assessment of glycerol and glucose metabolism, we will use non-parametric paired t-test for comparison using a convenience sample for this pilot feasibility study.
- Descriptive differences between fasting ketone levels, insulin to carbohydrate ratios, insulin to protein ratios, insulin sensitivity factors, total daily insulin dose will also be reported.
- Glucagon, glucose, and beta-hydroxybutyrate response to arginine stimulation
- Questionnaires will evaluate changes in diabetes treatment satisfaction, nutritional knowledge, and diabetes distress over time. These analyses will help determine satisfaction with the study diet when compared to a standard diet. Due to the pilot nature of the study, these analyses will be exploratory, and we will not adjust for the number of comparisons.
- Meal content will be determined by using the ASA24 program (https://asa24.nci.nih.gov). Macronutrient content of each diet will be reported.
- Safety Analysis: Frequency of diabetic ketoacidosis and severe hypoglycaemia events will be assessed in all participants, including those whose data do not meet evaluability criteria.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒**N/A**

B. DRUGS/BIOLOGICS ☐**N/A**

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*: **N/A**

2. **Background Information:** All substances are non-radioactive and have been extensively used in pediatric research in the last 15 years by our team with no side effects or adverse effects. Recent studies involving minors using glucose and glycerol isotopes performed by members of our research team are listed below.

HIC #	Age group	Isotope	Dosage	Isotope	Dosage
0102012241	8 years-adult	6,6-D_2-glucose*	0.4 g/m^2 bolus	D_5-glycerol	0.6 μmol/m^2 4 μmol/m^2·min
1604017607	12-30 years	6,6D_2-glucose*	0.4 g/m^2 bolus	D_5-glycerol	0.6 μmol/m^2 4 μmol/m^2·min
1306012200	≥ 12 to ≤ 20 yrs Type 1 Diabetes	6,6-$^2H_2$-glucose	4.5 mg/kg bolus 0.03 mg/kg/min	$^2H_5$-glycerol	1.6μmol/kg, 0.11 μmol /kg/min
1509016531	12-35 years Type 1 Diabetes	6,6-$^2H_2$-glucose	3.5 mg/kg bolus 0.04 mg kg/min		
2000023149	12-16 years 18-24 years	6,6-$^2H_2$-glucose	4.5 mg/kg bolus 0.06 mg/kg/min	$^2H_5$-glycerol	1.6μmol/kg, 0.11 μmol /kg/min

*Stable phases will use 20% glucose infusion containing 6,6,-D2-glucose at an enrichment of approximately 3%

PMID	Age group	Isotope	Dosage	Isotope	Dosage
30020457	14-17 years Type 1 Diabetes	6,6-$^2H_2$-glucose	4.5 mg/kg 0.03 mg/kg/min	$^2H_5$-glycerol	1.6μmol/kg, 0.11 μmol /kg/min

3. **Source:** There is no study drug (treatment) for this protocol. However, isotopes will be obtained from Cambridge Isotopes, Cambridge, MA), which is routinely audited internally by its QA department and externally by customers, notified bodies, and regulatory agencies (e.g. FDA). Isotopes will be stored in the Investigational Pharmacy and will be prepared before the subjects undergo tests.

a) Is the drug provided free of charge to subjects? ☒**YES** ☐**NO**
If yes, by whom? **Funding for the study**

1. **Storage, Preparation and Use:** The glycerol isotope will be kept with Yale-New Haven Hospital Investigational Drug Service, which will keep all documentation. The IDS will prepare preparations of isotopes before each study and store it in the med room in the YCCI. Pyrogen and sterility are tested and documented by Cambridge Isotopes before shipping to us.

Check applicable Investigational Drug Service utilized:

☒ **YNHH IDS** ☐ **CMHC Pharmacy** ☐ **West Haven VA**
☐ **PET Center** ☐ **None**
☐ **Other:**

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

2. **Use of Placebo:** ☒**Not applicable to this research project**

3. **Continuation of Drug Therapy After Study Closure** ☒**Not applicable to this project**

B. DEVICES ☒**N/A**

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: **10-20 youth will be studied,** which includes at least 4 adults over the age of 18.

b. If this is a multi-site study, give the total number of subjects targeted across all sites: **N/A**

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers
☐ Posters
☐ Letter
☒ Medical record review*
☐ Departmental/Center newsletters
☐ YCCI Recruitment database
☐ Internet/web postings
☐ Mass email solicitation
☐ Departmental/Center website
☐ Departmental/Center research boards
☐ Web-based clinical trial registries
☒ Social Media (Twitter/Facebook): Twitter, Facebook, Instagram
☐ Radio
☐ Telephone
☐ Television
☐ Newspaper
☒ Clinicaltrails.gov
☒ Other: Yale Children's Diabetes Program

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. **Eligible participants will be identified through the Yale Children's Diabetes Program and Yale Diabetes Clinics by review of medical records and recommendation of clinicians. Eligible participants will also be recruited through social media and through JDAT.**

b. Describe how potential subjects are contacted. **The participant will be informed of the study by their usual diabetes healthcare team, or by a HIPAA-compliant e-mail, or phone call if there is a clinical relationship with a member of the research team**

c. Who is recruiting potential subjects? **Laura Nally, MD, William Tamborlane, MD, Amy Steffen, RN, Kate Weyman, APRN, Jennifer Sherr, MD, Elaine Tichy, PA, Michelle van Name, MD, Nicola Santoro, MD, PhD, Stephan Seibel, MD, PhD.**

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship. **Participants will be recruited from the Yale Children's Diabetes Program and the research team will have an existing clinical relationship with these subjects.**

Recruitment process outline for clinic patients:

i. The medical records of patients in our clinic are reviewed to determine eligibility
ii. The medical provider of the patient will be contacted whenever possible to determine whether contact from the study team is appropriate.
iii. Eligible patients are contacted in person whenever possible, or via phone or email to inform them of potential participation. Alternatively, potential participants are informed of the study during a clinic visit.
iv. Potential participants who respond with interest in learning more will be provided potential study dates, consent forms to review, and contacted via phone to discuss the study in more detail
v. Potential participants/family will then have an in-person meeting with a study team member (approved for consenting), to review the consent/assent forms in detail. If the potential participant/family wish to proceed, the forms are signed.
vi. Potential participants will be recruited through social media (Twitter, Facebook, Instagram).

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☒ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: **To determine whether patients will be eligible for this study and thus consent procedures, the study team will review the medical records.**

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: **Some potential subjects may call or email after learning about the trial by word of mouth. We can ask some basic screening questions about age, date of diagnosis etc. before scheduling an enrollment visit to do further screening to determine study eligibility.**

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Potential participants who express interest in the study will be given a copy of the Consent Form/Parent Permission/Assent Form, asked to review, and then given the opportunity to discuss the study with the investigators in detail. For part 1 of the study, consent will be performed over the phone or virtually. This will be done either via RedCap or by emailing/mailing the consent form and having the participant email/mail the signed consent form back to the researcher. For part 2 of the study, consent will take place in person. The investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent. It will of course be stressed that participation is voluntary, and non-participation will not affect continuing care at the Yale Children's Diabetes Program. The participant will have the right to refuse to participate or to withdraw at any time.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Subjects will have a face-to-face meeting (part 1 will be ***in person or virtually*** over the phone or via Skype, Zoom, FaceTime or Doximity Dialer enabling video calls) with an Investigator and/or Study Personnel to address questions about the study rationale, procedures, risks and benefits. In order to identify and clarify any misconceptions, subjects will be encouraged to describe the research procedures and their associated risks in their own words, followed by correction of any errors by an Investigator or Study Personnel.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   Write here

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of <u>signed</u> consent:**

☒ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☒ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☐ **Requesting a waiver of consent:**

☐ **<u>Recruitment/Screening</u> only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ **<u>Entire Study</u>**

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver?
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?
  <u>N/A</u>

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? **Protected health information that will be collected and used for the research will include the research study records, medical records, blood sugars, services provided in connection with this study, the entire research record and any medical records held by Yale New Haven**

Hospital and the Yale School of Medicine, medical history of diabetes and other conditions that may affect eligibility for study participation.

2. How will the research data be collected, recorded and stored? **Clinical research forms will be created to allow for collection of data from schools and for study visits. Our study team is very experienced in collecting data and maintaining study databases, as we regularly conduct clinical trials. Study records will be maintained in Microsoft Excel databases, on university computers which are encrypted and served by a regular back up service. All study staff, office, and computers are HIPPA compliant.**

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   The list of names of the study subjects and their assigned code numbers will be kept in a locked file cabinet or password-protected computer file by study team members. Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. All individuals involved in the conduct of this study will be trained on HIPAA privacy regulations and will receive human subject protection training. The principal investigator will periodically monitor the methods and procedures described herein to ensure proper use and that continued protections are in place and being followed.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. **It is likely that data from this study will be published in scientific and medical journals and presented at scientific and medical conferences. In all such cases, project data will be presented in such a way that no participant could possibly be identified. Data will be de-identified at end of study prior to study termination.**

6. If appropriate, has a Certificate of Confidentiality been obtained? **N/A**

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Participants may experience improved glycemic control by participating in the study.
Long-term benefits of this research are a generalizable understanding of the changes of insulin resistance related to obesity and puberty in youth with T1D, which will help to inform future treatment strategies.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative to participating in this study is non-participation. Subjects who choose not to participate may continue their normal care in the Yale Pediatric Diabetes Program. There are no risks of non-participation.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Part 1: Participants will receive a total of $75 total for participating in the full study.

   Part 2: To help offset the cost of the subjects' participation in the study, they will receive $50 for each of the HRU/CSRU visits. For each day that the participants take photos of their food and speak with study staff regarding dietary recall, they will receive $5. The total compensation a subject could potentially earn is $160.

3. **Costs for Participation (Economic Considerations):** The costs of all study-specific equipment, such as the blood ketone meter and ketone test strips, will be covered by the study. Since continuous glucose monitors, glucometers and glucose test strips are part of routine diabetes care, these will be prescribed. Clinical lab HbA1c is standard of care and will be billed through the participant's insurance and will not be covered by the study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   a. Will medical treatment be available if research-related injury occurs? *Yes*
   b. Where and from whom may treatment be obtained? *Research staff or YNHH staff if necessary*
   a. Are there any limits to the treatment being provided? Injuries caused directly by participation in the study. There will be no payment for lost wages and/or direct or indirect losses.
   a. Who will pay for this treatment? Subjects will be responsible for the costs of such medical care that is not covered by their own health insurance.
   a. How will the medical treatment be accessed by subjects? By notifying Research Team members

   If injury should occur during any of the procedures, the overseeing physician and the study nurse will attend to the immediate needs of the patient. Should any acute care visit (i.e. emergency room or outpatient clinic), hospital admission or chronic care be necessary, the subject's medical insurance will be responsible for covering any incurred charges.

IMPORTANT REMINDERS

Will this study have a billable service? **Yes** ☐ **No**☒

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☒ No ☐**

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☒ No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐ No ☒**

c. Will a novel approach using existing equipment be applied? **Yes ☐ No ☒**

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

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