PROTOCOL TITLE**: Effect of liraglutide on glycemic control, glucagon secretion and inflammatory markers in adolescents with Type 1 diabetes mellitus.**

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INSTRUCTIONS: Complete Research Protocol (HRP-503)

- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable for the response. For example, most behavioral studies would answer all questions in section 30 with words to the effect of "drugs and medical devices are not used in this study."*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it will not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Response: Effect of liraglutide on glycemic control, glucagon secretion and inflammatory markers in adolescents with Type 1 diabetes mellitus.

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER:

Include the version number of this protocol.

Response: 3

DATE:

Include the date of submission or revision.

Response: August 15, 2019

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Response: N/A

Table of Contents

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

Response: Type 1 diabetes is one of the most common chronic diseases of childhood. It is caused by autoimmune destruction of the insulin-producing pancreatic beta cells. Patients with Type 1 diabetes are at high risk for development of long-term complications related to hyperglycemia. Individuals with this disease are completely dependent on insulin for survival. While significant advances have been made in technological support for improving diabetes control, insulin remains the only effective treatment for Type 1 diabetes.

1.2 State the hypotheses to be tested.

Response: The main objective of this study is to test the hypothesis that a long-acting glucagon-like peptide 1 analog, liraglutide, will improve mean weekly blood sugars in adolescents and young adults with Type 1 diabetes.

Background

1.3 Describe the relevant prior experience and gaps in current knowledge.

Response: **Background:** Type 1 diabetes (T1DM) affects approximately 1:500 children and represents the major form of diabetes in the pediatric population (1). Diagnosis of T1DM is based on symptoms consistent with hyperglycemia (polyuria, polydipsia, and weight loss) and elevated blood sugars. Diagnosis of T1DM is confirmed by measuring serum autoantibodies against insulin and other beta-cell proteins. Subcutaneous insulin is the mainstay of diabetes care; however, ability to achieve optimal glycemic control is impacted by multiple factors including diet, exercise, and psychosocial barriers.

The Diabetes Control and Complications Trial and follow-up EDIC trial were landmark studies demonstrating that improving glycemic control significantly reduces the risk of both micro and macro-vascular disease (2). While technologic advances in blood sugar monitoring, insulin analogs and insulin delivery devices have been made, it is estimated that less than 40% of individuals meet recommended glycemic standards as set forth by the American Diabetes Association; these estimates may be lower in the pediatric population. Thus, adjuvant pharmacologic therapies that improve glycemic control are being tested in patients with T1DM.

Incretin hormones are a class of intestinal peptides that are released in response to nutrient intake (3). The best described incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones act at the level of direct stimulation of pancreatic β-cell function and through extra-pancreatic mechanisms. They primarily potentiate glucose-dependent insulin secretion from the β-cell; other β-cell effects include increasing insulin biosynthesis, stimulating β-cell replication, and preventing apoptosis. Secondary effects of incretin hormones include suppression of glucagon secretion, inhibition of gastric emptying, and potentiation of hepatic glucose uptake (3).

Currently, there are two GLP-1 analogs approved by the Food and Drug Adminstration as adjuvant treatment of Type 2 diabetes mellitus in adults (> 18 years) who fail to reach glycemic targets with metformin and/or oral hypoglycemic agents. The

two drugs – exenatide (BID) and liraglutide (QD) are administered subcutaneously. They have been demonstrated to improve glycemic control in this population and, in some individuals, lead to sustained weight loss.

This study aims to determine whether acute exposure to liraglutide decreases the mean weekly blood glucose levels in adolescents with T1DM. In addition, we will determine whether liraglutide decreases glucose excursions following a meal challenge. *The overall hypothesis to be tested is that short-term exposure (7 days) to liraglutide improves glycemic control in adolescents/young adults with T1DM treated with continuous subcutaneous insulin infusion.*

Specific Aim 1: Determine whether liraglutide decreases the mean weekly blood glucose levels in adolescents/young adults with T1DM. *Hypothesis: Mean weekly blood glucose will decrease when liraglutide is used as an adjuvant therapy to insulin in individuals with T1DM.* Subjects will wear continuous glucose monitors to measure interstitial glucose as a surrogate for blood glucose. The CGM will be worn for 7 days pre- and post- daily liraglutide treatment. Data will be downloaded and mean weekly blood sugars will be determined.

Specific Aim 2: Determine whether liraglutide treatment decreases blood glucose excursion during mixed meal tolerance test in adolescents/young adults with T1DM. *Hypothesis: Post-prandial blood glucose excursions are attenuated with liraglutide treatment.* Mixed meal tolerance tests will be performed with and without pre-treatment with liraglutide. Blood glucose levels will be measured at set time points during the test and blood glucose excursions as well as blood glucose AUC in response to the meal challenge will be calculated.

Specific Aim 3: Determine whether glucagon secretion decreases during mixed meal tolerance test in subjects treated with liraglutide. *Hypothesis: Glucagon secretion following a meal challenge is suppressed in response to liraglutide treatment.* Serum samples will drawn during mixed meal tolerance test performed with and without pre-treatment with liraglutide. Glucagon will be measured by ELISA and glucagon secretion AUC will be calculated.

Specific Aim 4: Determine whether liraglutide treatment leads to a reduction in total daily insulin dose.
Hypothesis: Improved glycemic control can be attained with lower total daily insulin requirements in subjects treated with liraglutide. Total daily insulin dose will be determined for seven days before and after initiation of liraglutide therapy. Insulin dose/kilogram body weight will be determined and evaluated in relationship to changes in mean weekly blood sugars.

In addition to the specific aims outlined above, the following exploratory aims will be addressed:

Exploratory Aim 1: Determine the side effect profile of liraglutide in adolescents/young adults with T1DM. *Hypothesis: Side effect profile of short-term liraglutide treatment in this population will be similar to that reported in adults.* Study subjects will keep a diary reporting hypoglycemic events and other potential adverse effects. Type, number, and rate of adverse events will be determined.

Exploratory Aim 2: Determine if there is a difference in caloric intake with liraglutide treatment in adolescents/young adults with T1DM. *Hypothesis: Caloric intake decreases in response to liraglutide treatment.* Subjects will keep a 4 day food record before and after initiation of liraglutide. Total caloric intake will be calculated, and within subject differences in caloric intake before and after liraglutide treatment will be determined.

Exploratory Aim 3: Determine if liraglutide treatment alters serum inflammatory markers in subjects with T1DM. *Hypothesis: Acute liraglutide therapy decreases serum levels of C-reactive protein and increases adiponectin levels in subjects with T1DM.* Serum samples before and after liraglutide therapy will be drawn and levels of inflammatory markers will be measured. Within subject differences will be determined.

Describe any relevant preliminary data.

Response: Although individuals with T1DM may not benefit from the direct β-cell actions of GLP-1 analogs given the targeted autoimmune component of the disease, the impact on glucagon secretion and extra-pancreatic effects may improve overall glycemic control in this population. At least two studies have reported data testing the efficacy of GLP-1 analogs in individuals with T1DM. Heptulla et al. reported significant reductions in glucose excursions following a standard meal test in adolescents and young adults (n = 8, age 13-22) treated with a single dose of exenatide (4). Varanasi et al. reported that mean weekly glucose levels decreased significantly in adults with well-controlled T1DM (mean HbA1c = 6.4%) treated with daily liraglutide for 1 week (5). These findings suggest that GLP-1 analogs may represent potential therapeutic adjuvants to improve glycemic control in patients with T1DM.

1.4 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Response: Optimal diabetes control decreases the risk of long-term micro- and macro vascular complications in individuals with diabetes. Currently the only FDA approved therapy for management of T1DM is insulin, delivered either subcutaneously or via inhalation. The addition of therapies to decrease risk of glucose excursions at mealtimes would offer significant benefits to diabetes care.

1.5 Include complete specific citations/references.

References:

1. Bell RA, Mayer-Davis EJ, Beyer JW, D'Agostino RB, Jr., Lawrence JM, Linder B, et al. (2009) Diabetes in non Hispanic white youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care.32 Suppl 2:S102-11.
2. http://diabetes.niddk.nih.gov/dm/pubs/control/
3. Drucker DJ (2006) The biology of incretin hormones. Cell Metabolism 3:153-165.
4. Raman VS, Mason KJ, Rodriguez LM, Hassan K, Yu X, Bomgaars L, Heptulla RA (2010) The role of adjunctive exenatide therapy in pediatric type 1 diabetes. Diabetes Care. 33: 1294-1296.

5. Varanasi A, Bellini N, Rawal D, Vora M, Makdissi A, Dhindsa S, Chaudhuri A, Dandona P (2011) Liraglutide as additional treatment in type 1 diabetes. Eur J Endocrin epub ahead of print.

2.0 Inclusion and Exclusion Criteria

2.1 Describe the criteria that define who will be included or excluded in your final study sample.

Characteristics of the Research Population

- Gender of Subjects: Male and female subjects
- Age of Subjects: 15 – 21 years
- Racial and Ethnic Origin: All racial and ethnic groups will be included
- Inclusion Criteria
  - Adolescents and young adults followed by the UBMD Pediatrics, Division of Endocrinology/Diabetes Center.
  - Diagnosis of T1DM greater than 1 year
  - Insulin regimen – continuous subcutaneous insulin infusion with or without concurrent use of continuous glucose monitoring device
  - HbA1c <10%
- Exclusion Criteria
  - Previous exposure to liraglutide
  - History of abdominal surgery
  - Gastrointestinal reflux disease
  - History of acute or chronic pancreatitis
  - History of alcohol abuse or unwillingness to abstain from alcohol during the study
  - Unwilling to wear a continuous glucose monitoring device during the study.
  - History of thyroid cancer
  - Family history of Multiple Endocrine Neoplasia 2B syndrome
  - Pregnant/breastfeeding females
  - Individuals with antibody-negative insulin requiring diabetes that is consistent with Monogenic Diabetes of Youth
  - Individuals with steroid induced or cystic fibrosis related diabetes.
  - Non-English speaking subjects

2.2 Describe how individuals will be screened for eligibility.

Response:

Recruitment: Subjects will be recruited from the UBMD Pediatrics, Division of Endocrinology/Diabetes clinic.

2.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response: N/A

2.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

Response: We will not be including non-English speaking individuals in this study for the following reasons 1) pilot study; 2) unfunded

3.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

3.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

Response: N/A

4.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

4.1 Describe when, where, and how potential subjects will be recruited.

Response: N/A

4.2 Describe the methods that will be used to identify potential subjects.

Response: N/A

4.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: N/A

5.0 Multi-Site Research (Multisite/Multicenter Only)

5.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Response: N/A

5.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response: N/A

6.0 Study Timelines

6.1 Describe the duration of an individual subject's participation in the study.

Response: The total duration of time for participation is 2 weeks. This study involves three visits.

6.2 Describe the duration anticipated to enroll all study subjects.

Response: 4 years

6.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Response: 60 months

7.0 Study Endpoints

7.1 Describe the primary and secondary study endpoints.

Response: For statistical purposes, the **primary endpoint** of the study is to detect a difference between untreated and treated periods in the change from baseline in mean weekly blood glucose concentrations. The statistical analysis will be carried out using

analysis of variance (ANOVA) and tested at the 0.05 level. The results will be computed as mean±SD.

The secondary end points based on glycemic changes will include the difference from baseline in standard deviations of the mean weekly glucose concentrations, mean fasting blood glucose concentrations, the duration of time spent in hyperglycemia (>150mg/dl, > 200mg/dl, > 250mg/dl) and hypoglycemia (< 70mg/dl, < 40mg/dl), and insulin dosage. A reduction in the area under curve following the meal will constitute another secondary end point. Within subject comparisons of the magnitude of change from baseline will also be made for these glycemia related secondary endpoints using student's t-test. Comparisons for these and the primary endpoints will also be made using the paired *t*-test or Wilcoxson's test for paired data for each subject. Additional secondary end-points of the study will be change from baseline in 1) mean weekly blood glucose 2) glucagon area under the curve concentrations following meal challenge 3) change in daily insulin dose (total dose and units/kg) 4) caloric intake based on 4 day food records and 5) change in serum adiponectin and CRP levels before and after initiation of liraglutide treatment. The relation between change in postprandial sugars, glucagon, and total daily insulin dose will be studied by regression analysis to evaluate the relative contribution of each of these parameters to the improvement in post-prandial blood sugars.

Variables of Interest:

Visit 1

- Age, gender, height, weight, total daily insulin dose, HbA1c, insulin pump settings
- Total daily insulin dose
- History of severe hypoglycemic events,
- History of pancreatitis, alcohol use, thyroid cancer, family history of MEN 2B

Visit 2

- Insulin pump settings
- Total daily insulin dose
- Food diaries
- Download of continuous glucose monitor – mean weekly blood sugars
- Blood sugar records with reports of hypoglycemia
- Mean blood glucose excursion, glucagon release, and serum inflammatory markers during mixed meal tolerance test

Visit 3

- Insulin pump settings
- Total daily insulin dose
- Food diaries
- Download of continuous glucose monitor – mean weekly blood sugars
- Blood sugar records with reports of hypoglycemia
- Adverse effects
- Mean blood glucose excursion, glucagon release, and serum inflammatory markers during mixed meal tolerance test

Describe any primary or secondary safety endpoints.

Response: Adverse effects including nausea/vomiting, anorexia. Injection site reactions/pain. Rates of hypoglycemia. Clinical or biochemical evidence of pancreatitis.

8.0 Procedures Involved

8.1 Describe and explain the study design.

Response: This is a pilot unblinded prospective within subject investigational-drug intervention trial.

8.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Response:

Summary of Research Design and Procedures:

The proposed study will involve three visits. The study will involve an initial screening meeting at which time the subject will be invited to join the study and sign informed consent. During the Visit 2 and Visit 3, mixed meal tolerance tests will be performed.

Visit 1 Screening Day (day 0):

- Review the subject's medical history and family medical history
- Review subject's blood sugars and insulin pump settings
- Measure height, weight, blood pressure and heart rate.
- The principal investigator will perform a physical exam.
- If hemoglobin A1c level is not recorded in the medical record within 2 weeks of visit 1, this test will be performed.
- Record mean total daily insulin dose (previous 72 hours) from insulin pump.
- Subjects will be advised to wear his/her continuous glucose monitor (CGM) for the next two weeks, changing sites as indicated by the manufacturer.
- For subjects who do not have a CGM, we will insert the Abbott Freestyle Libre Profession Device. This device will monitor glucose levels throughout the entire study period. Subjects will be advised to check blood sugars at least 4 times per day and at any occasion when symptoms of hypoglycemia develop.
- Subjects will be asked to keep a record of any episodes of hypoglycemia.
- Subjects will be asked to keep a 4 day food record (three days, 1 weekend day).
- Subjects will be advised to follow their usual diabetes care plan with respect to carbohydrate counting, diet and exercise.

Visit 2 (Day 7): Subjects will come fasting for this visit. They will bring the food records and diary of hypoglycemia to this visit. This visit will take approximately 4 hours. At this visit, the following procedures will be performed:

- Records of blood sugars and CGM data will be obtained from subjects wearing personal CGMs
- Subjects wearing the Freestyle LibrePro system will continue wearing the device unless it became dislodged during the study. A new device will be placed in this case.
- Blood sugars and insulin pump settings will be reviewed.
- Record mean total daily insulin dose (previous 72 hours) from insulin pump.
- A Mixed Meal Tolerance test will be performed (see below)

- Insulin pump settings will be adjusted to decrease the risk of hypoglycemia during liraglutide treatment. Basal rates will be decreased by 25% and meal boluses will be decreased by 33%.
- The first dose of liraglutide will be given at the study site. Subjects will be given 0.6 mg subcutaneously. Subjects will be taught how to use the delivery device at this visit.
- Subjects will be advised to take 0.6 mg of liraglutide subcutaneously every morning at about the same time.
- Subjects will be given a diary and be asked to record any episodes of hypoglycemia, as well as any other side effects such as nausea, decrease in appetite, and other problems.
- Subjects will be asked to keep a 4 day food record (three days, 1 weekend day).
- Subjects will be provided with contact information for the principal investigator in case of any problem or untoward side effect. They will be asked to notify the study staff for persistent low blood sugar (BS < 70 mg/dL), persistent high blood sugar (BS > 250 mg/dL), or urine ketones.
- Subjects will be advised to return to clinic in 7 days.

Visit 3 (Day 14): This is the final study visit. Subjects will come fasting for this visit. The subject will not take liraglutide prior to coming to this visit but will bring the study drug to the visit. Subjects will bring the food records and diary of hypoglycemia to this visit. This visit will take approximately 4 hours. At this visit, the following procedures will be performed:

- Records of blood sugars and CGM data will be obtained.
- Freestyle LibrePro device will be removed and data obtained.
- Blood sugars and insulin pump settings will be reviewed
- Record mean total daily insulin dose (previous 72 hours) from insulin pump.
- Liraglutide (0.6 mg subcutaneously) will be administered 45 minutes prior to the Mixed Meal Tolerance Test
- A Mixed Meal Tolerance test will be performed (see below).
- All study drug will be returned.
- Subjects will be advised to resume previous basal rates and carbohydrate ratios within 48 hours of final study visit.

Mixed Meal Tolerance Test (MMTT). This test will be done at Visit 2 and Visit 3. The MMTT is a test to measure blood sugar levels in response to a meal and the amount of glucagon that is produced in response to changes in blood sugar. Prior to the test, a catheter will be placed to reduce the number of needle sticks during the test. Subjects will drink 240 ml of a high protein nutrition drink (BOOST). An appropriate amount of insulin for the carbohydrate intake of the meal challenge will be administered via insulin pump to taking the drink. Blood will drawn once before the meal and 8 times during the meal over 3 hours. The total amount of blood that will be drawn is ~ 20 teaspoons (100 mL).

The following parameters will be drawn for measurement during the MMTT

- Blood Glucose
- Glucagon
- Serum inflammatory mediators

Blood samples (5 ml each) will be collected into fluoride (grey top) for glucose measurement and serum separator tubes for serum samples. Glucose levels will be transported to the Kaleida Health Department of Pathology and Laboratory Medicine for analysis. Samples for glucagon and serum inflammatory markers will be kept at room temperature prior to centrifugation. Centrifugation will occur within one to two hours after collection of the samples. The blood samples will be centrifuged for ten minutes at room temperature at a relative centrifugal force of 1500xg. Serum samples will be aliquoted and frozen at -

20ºC. All samples will be labeled with subject name, date of birth, subject number, date of collection, and time of collection. Subject number will be assigned sequentially based on entry into the study. All relevant data regarding the samples will be entered into a computer database . Sample assays will be performed in duplicate to control for intra-assay variability.

8.3 Describe procedures performed to lessen the probability or magnitude of risks.

Response: All study tasks will be performed in a quiet and private room. Subjects will be advised of potential adverse events and provided with contact information for Dr. Mastrandrea. Insulin doses will be lowered in order to decrease the risk of hypoglycemia during the liraglutide treatment week.

8.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Response: Study drug = liraglutide, a GLP-1 analogue. This drug is approved for management of Type 2 diabetes in adults. The liraglutide pen device will be returned following completion of the study, and any remaining drug will be destroyed at the study site by the study investigators. The principal investigators will be responsible for ensuring that the liraglutide devices will only be used by individuals who have provided consent and who have agreed to participate in the study. See attached FDA IND exemption for this study.

8.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Response:

A data collection tool (attached) will be used to collect the following data from the patient or from the medical record:

- Age (Year-months; based on date of birth)
- Sex
- Date of diabetes diagnosis
- Insurance Type
- Height (cm) and weight (kg)
- Body mass index (BMI)
- Blood pressure
- Hemoglobin A1c (POS)
- Insulin regimen and daily insulin use
- Other medications
- Side effect diary
- 4 day food records

In addition, the insulin pump download and blood glucose monitor downloads will be reviewed to collect the following information:

For all subjects:

- Number of blood sugar checks/day (average of 7 days prior to visit)
- Total basal dose
- Total daily insulin dose
- %basal/%bolus
- Boluses recorded/day
- Grams of carbohydrate recorded/day

Data will be recorded on the source document that carries the subject identifier number. Data will then be transferred to an Excel spreadsheet – no identifying data will be recorded in this spreadsheet.

8.6 What data will be collected including long-term follow-up.

Response: See above.

8.7 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response: N/A

9.0 Data and Specimen Banking

9.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.

Response: Data will be stored on a password-protected computer in a locked office. The principal investigator will have access to the data for data entry and analysis. Biological specimens collected during the MMTT will be stored in -80°C freezer at Jacobs School of Medicine, 5th floor. Only Dr. Mastrandrea or research assistants will have access to these specimens. Data will be stored until study completion. Samples will be stored until study completion.

9.2 List the data to be stored or associated with each specimen.

Response: Data will be stored with subject identifier number. Specimens will have recorded subject identifier, as well as time point during MMTT, and date of collection.

9.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: No data will be released.

10.0 Data Management

10.1 Describe the data analysis plan, including any statistical procedures.

Response: Response: For statistical purposes, the **primary endpoint** of the study is to detect a difference between untreated and treated periods in the change from baseline in mean weekly blood glucose concentrations The statistical analysis will be carried out using analysis of variance (ANOVA) and tested at the 0.05 level. The results will be computed as mean±SD.

The secondary end points based on glycemic changes will include the difference from baseline in standard deviations of the mean weekly glucose concentrations, mean fasting blood glucose concentrations, the duration of time spent in hyperglycemia (>150mg/dl, > 200mg/dl, > 250mg/dl) and hypoglycemia (< 70mg/dl, < 40mg/dl), and insulin dosage. A reduction in the area under curve following the meal will constitute another secondary end point. Within subject comparisons of the magnitude of change from baseline will also be made for these glycemia related secondary endpoints using student's t-test. Comparisons for these and the primary endpoints will also be made using the paired *t*-test or Wilcoxson's test for paired data for each subject. Additional secondary end-points of the study will be change from baseline in 1) mean weekly blood glucose 2) glucagon area under the curve concentrations following meal challenge 3) change in daily insulin dose (total dose and units/kg) 4) caloric intake based on 4 day food records and 5) change in serum adiponectin and CRP levels before and after initiation of liraglutide treatment. The relation between change in postprandial sugars, glucagon, and total daily insulin dose will be studied by regression analysis to evaluate the relative contribution of each of these parameters to the improvement in post-prandial blood sugars

10.2 Provide a power analysis.

Response: A previous study (5) in adults with well-controlled diabetes demonstrated that liraglutide treatment decreased mean weekly blood sugars by 22 mg/dL. Based on these results, *a priori* power analysis indicates that 9 subjects will need to be enrolled in the study to detect a change in mean weekly blood sugars of 22 ± 20 mg/dL between untreated and treated periods with 80% power and alpha error of 0.05 (paired t-test). We will enroll up to 12 subjects for this study.

10.3 Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Response: All primary data collection tools will be stored in Dr. Mastrandrea's office. All personal information, signed consents/assents and patient blood sugar logs/food diaries will be stored in a locked filing cabinet in principal investigator's locked office. Data will be entered into a password protected Excel Spreadsheet. Access to the computer system is also password protected and only members of the study team will have access to the electronic data. All members of the team have completed CITI and GRP training. Data will not be transmitted.

10.4 Describe any procedures that will be used for quality control of collected data.

Response: Dr. Mastrandrea will be responsible for review of data on a regular basis to ensure that collected data is being entered correctly.

10.5 Describe how data and specimens will be handled study-wide:

Response: Data will be entered electronically in a timely manner. Downloads of meters/pumps are scanned into the medical record as part of standard of care.

10.6 What information will be included in that data or associated with the specimens?

Response: See data collection tool. Each subject will be assigned a unique study identification number.

10.7 Where and how data or specimens will be stored?

Response: All personal information, signed consents/assents and patient blood sugar logs/food diaries will be stored in a locked filing cabinet in principal investigator's locked office. Data will be stored on a password-protected computer in Dr. Mastrandrea's office.

10.8 How long the data or specimens will be stored?

Response: Data will be stored for 5 years after the completion of the study.

10.9 Who will have access to the data or specimens?

Response: Study data will be stored on a password-protected computer that is limited to the principal investigator and co-investigators.

Who is responsible for receipt or transmission of the data or specimens?

Response: Dr. Mastrandrea

10.10How data and specimens will be transported?

Response: Data will be stored on password-protected computer. Data will not be transported.

11.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

11.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Dr. Mastrandrea is responsible for review of data on a regular basis to ensure that collected data is being entered correctly. All unforeseen events during the study tasks will be reported immediately to the principal investigator; if necessary, they will be reported to the IRB.

11.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Data related to study tasks will be reviewed.

11.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Safety information will be documented on the data collection tool as necessary.

11.4 Describe the frequency of data collection, including when safety data collection starts.

Response: Dr. Mastrandrea is responsible for collection and review of all data.

11.5 Describe who will review the data.

Response: Dr. Mastrandrea

11.6 Describe the frequency or periodicity of review of cumulative data.

Response: see above

11.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: Number of severe hypoglycemic events will be documented. The rate of severe hypoglycemia will be compared to historical data.

11.8 Describe any conditions that trigger an immediate suspension of the research.

Response: Episode of pancreatitis.

12.0 Withdrawal of Subjects

12.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Response: A subject may be withdrawn from the study if they are having significant side effects to liraglutide – nausea/vomiting, severe hypoglycemia. In addition, a subject may be withdrawn if they are having difficulty completing the study tasks essential for data collection.

12.2 Describe any procedures for orderly termination.

Response: Subject data will not be included in the analysis, and the subject will be replaced. All subjects will receive study compensation even if they are not included in the finals study analysis.

12.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Response: If a subject is withdrawn from the research prior to de-identification of data, no data will be used for the subject. The data will be expunged and the subject will be replaced. If a subject withdraws from the study after de-identification of data, no further data will be collected for that subject. However, any data already collected may be included in the final analysis.

13.0 Risks to Subjects

13.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Response: **Types of Risk:**

Important Safety Information (see attached product information): In animal studies, liraglutide caused rats and mice to develop thyroid tumors, some of which were cancers. It is not known whether liraglutide causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in humans. Subjects with a history or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia syndrome type 2 (MEN2) will not be enrolled in this study.

Treatment with GLP-1 is associated with inflammation of the pancreas (pancreatitis) which may be severe and can lead to death. Certain conditions increase the risk of developing pancreatitis including history of pancreatitis, gallstones, alcoholism, or high triglyceride levels. We will review the subject's medical record to assess for any of these risk factors. In addition, subjects will be excluded if they have a history of pancreatitis. While taking liraglutide, the subjects will be counseled to notify study staff if they develop severe abdominal pain. Should this occur, they will be advised to discontinue liraglutide and testing for pancreatitis will be performed (serum amylase and lipase). Subjects will also be counseled not to consume alcohol while enrolled in this study.

Glucagon-like peptide 1 is an incretin hormone that is released in response to ingestion of food. Long-acting GLP-1 analogues and drugs which inhibit the metabolism of GLP-1 are FDA-approved as adjuvant therapy for the treatment of Type 2 diabetes. These drugs are currently not approved for use in the T1DM population. Individuals treated with GLP-1 analogues are at increased risk for hypoglycemia. It is recommended that patients treated with insulin secretagogue therapies (ie sulfonylureas), have their secretagogue dose decrease when GLP-1 analogue therapy is initiated. In this study, subjects have T1DM and are reliant on insulin for blood sugar control. In order to decrease the risk of hypoglycemia in this population, subjects will be counseled to decrease their basal insulin rates by 25% and their bolus insulin coverage for carbohydrates by 30% during the seven days when they are receiving liraglutide. All study subjects will be advised to check their blood sugar if they experience any symptoms consistent with hypoglycemia. They will be asked to contact the study team for persistent hypoglycemia while taking liraglutide. In addition, because insulin doses will be decrease significantly when liraglutide is initiated, there is the risk that subjects will experience hyperglycemia and may develop ketonuria. Subjects will be advised to contact the study team for persistent hyperglycemia and/or presence of urine ketones. The insulin dose will be increased to address this concern.

The most common side effects experiences by adults taking liraglutide include headache, nausea, and diarrhea. Nausea is most common when first starting liraglutide but generally decreases with time. Subjects may also feel less hungry while taking liraglutide. We will monitor for these and additional side effects during the study.

Physical Risks: In addition to the physical risks described above related to liraglutide, adverse events that are outlined in the informed consent include pain, bruising, or infection at the blood draw site. In addition, a subject may experience light-headedness or may faint during the MMTT. These events will be recorded and maintained as part of the study record. To decrease the likelihood of these risks, staff trained in performance in MMTT will perform the test and the subjects will be observed after the test. Subjects may develop a skin infection at the site of insertion of CGM. We will alert subjects to monitor for any redness or swelling at the site and advise them to call Dr. Mastrandrea. The principal investigators are responsible for ensuring that all adverse risks are recorded. The study will be performed in accordance with the ethical principles as outlined in the Declaration of Helsinki and are consistent with Good Clinical Practice.

Privacy Risks: There is a risk to privacy. The study tasks will be performed in a quiet, private office.

Risk of Loss of Confidentiality: There is a small risk of loss of confidentiality. The informed consent contains wording that complies with relevant data protection and privacy legislation. By signing the consent/assent, the subjects/parents/guardians authorize the collection, use, and disclosure of their study data by the principal investigators and by those who need the information for the study. The informed consent also explains that the study data will be stored in a computer database, with confidentiality maintained in accordance with national data legislation. The informed consent also explains that in order to verify data, it may be necessary to access the subject's medical record at a later time in the study. The computer database, informed consents, and all data will be secured within Dr. Mastrandrea's locked office within the Division of Pediatric Endocrinology.

Psychological Risks: Subjects may experience negative emotions if we are able to demonstrate that liraglutide has a positive effect on glycemia. Subjects will be aware of their blood sugars throughout the study and may feel a sense of loss when the drug is discontinued at the end of the study. At the onset of the study, we will counsel these subjects that this study is being performed to test the hypothesis that liraglutide improves mean weekly blood glucose levels. They will be made aware that the drug is not approved by the FDA for treatment/management of T1DM.

13.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Response: Subjects may experience a side effect to liraglutide that is previously undescribed.

13.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: N/A

13.4 If applicable, describe risks to others who are not subjects.

Response: N/A

14.0 Potential Benefits to Subjects

14.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Response: **Potential Benefits:** Subjects may benefit directly from this study by receiving intensified diabetes care and review of their blood sugars with subsequent adjustment of insulin doses. The subjects may also experience improvements in their blood sugars, albeit temporary, during the treatment phase of the study. The results of the study may be used to develop longer term, randomized, double-blind, placebo-controlled studies to test the efficacy of liraglutide in management of T1DM.

14.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

Response: See above

15.0 Vulnerable Populations

15.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response: HRP-416 has been reviewed. Children will have the opportunity to provide assent.

16.0 Community-Based Participatory Research

16.1 Describe involvement of the community in the design and conduct of the research.

Response: N/A

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

17.0 Sharing of Results with Subjects

17.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response: No results will be shared.

18.0 Setting

18.1 Describe the sites or locations where your research team will conduct the research.

Response: The research will be conducted at the UBMD Pediatrics, Division of Endocrinology/Diabetes clinic space at 1001 Main Street, Buffalo, NY. All study testing will be done in a designated private and quiet area. For some subjects, Visits 2 and 3 will take place at the University Commons, University Pediatrics Associates Suite 5, Amherst, New York.

18.2 Identify where your research team will identify and recruit potential subjects.

Response: The research team will identify potential subjects at their clinic visit at the Diabetes Center . During visit 1, eligibility for the study will be determined. The study protocol will be reviewed with the subject and parent/guardian. Informed consent will be signed by the parent/guardian or subject (age≥ 18 years) with assent provided by subjects under 18 years of age. Subjects will be provided copies of the consent/study protocol and will be advised to notify study staff if they choose not to participate in the study. Signed consents will be stored in a locked file cabinet in the PI's locked office. Subjects will be provided with copies of signed consents.

18.3 Identify where research procedures will be performed.

Response: All research procedures will be performed in a designated private and quiet research area in the UBMD Pediatrics, Division of Endocrinology/Diabetes clinic space at 1001 Main Street, Buffalo, NY. For some subjects, Visits 2 and 3 will take place at the University Commons, University Pediatrics Associates Suite 5, Amherst, New York.

18.4 Describe the composition and involvement of any community advisory board.

Response: N/A

18.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: N/A

19.0 Resources Available

19.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response: Response: The principal investigator is a board-certified pediatric endocrinologist with proper IRB training as well as HIPAA training. The research staff work in the diabetes clinics and have experience with type 1 diabetes. The research staff has IRB training as well as HIPAA training. Study staff has experience administering the study tasks to be completed by subjects. All staff has completed CITI and GRP training. The study staff has experience in performing MMTTs.

Describe other resources available to conduct the research: For example, as appropriate: N/A

19.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: The Diabetes Center outpatient clinic provides care for 325 patients in the proposed age range for the study. Of those, ~130 are managed with insulin pump therapy. This is the relevant population for recruitment.

19.3 Describe the time that you will devote to conducting and completing the research.

Response: We have dedicated research staff. Dr. Mastrandrea will provide 5% of her professional time towards management of this project. There are three study visits for each subject.

19.4 Describe your facilities.

Response: For obtaining consent, the UBMD Pediatrics Outpatient clinic will be utilized. It has 8 patient exam rooms, 1 vital room and 1 lab room. Our diabetes department has a private research rooms that will be used for study tasks. For some subjects, Visits 2 and 3 will take place at the University Commons, University Pediatrics Associates Suite 5, Amherst, New York.

19.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response: Dr. Mastrandrea will be available to discuss any questions/concerns related to the study.

19.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All personnel involved in the research will review the protocol, consent, and also attend any training to review study procedures

20.0 Prior Approvals

20.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response: N/A

21.0 Recruitment Methods

21.1 Describe when, where, and how potential subjects will be recruited.

Response: The subjects will be recruited from UBMD Pediatrics, Division of Endocrinology/Diabetes clinic space at 1001 Main Street, Buffalo, NY during their outpatient clinic visits. Clinic rosters will be reviewed prior to clinic to identify potential subjects.

21.2 Describe the source of subjects.

Response: All potential subjects receive their diabetes care at the UBMD Pediatrics Division of Endocrinology/Diabetes.

21.3 Describe the methods that will be used to identify potential subjects.

Response: Potential subjects will be identified either from a) outpatient clinic schedules 2) diabetes clinic. We will identify individuals with Type 1 diabetes for > 1 year who are managed with insulin pump and approach them regarding the study.

21.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: N/A

21.5 Describe the amount and timing of any payments to subjects.

Response: Subjects will receive a $25 gift card/study visit when they have completed the study procedures. The gift card will be received at the end of each study visit. In the case where a subject receives a gift card of $50 or greater, we will alert them that they will need to complete an IRS Form W-9.

22.0 Local Number of Subjects

22.1 Indicate the total number of subjects to be accrued locally.

Response: 12

22.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Response: We expect that all subjects who meet inclusion/exclusion criteria and sign informed consent/assent will complete the study.

23.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

23.1 Where and how data or specimens will be stored locally?

Response: Each subject will be assigned a unique study identification number. All study data will be de-identified. Downloads of meters/pumps will be stored in Dr. Mastrandrea's office. Data will be extracted from those records. Study data will be stored on a password-protected computer that is limited to the principal investigator.

If a subject receives a gift card of value $50 or greater, we will ask them to complete an IRS Form W-9. This form will be held confidentially in Dr. Mastrandrea's office and those responsible for administering the research funds.

23.2 How long the data or specimens will be stored locally?

Response: Data will be stored for 5 years after the completion of the study.

23.3 Who will have access to the data or specimens locally?

Response: Only study personnel.

23.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response: N/A

23.5 How data and specimens will be transported locally?

Response: N/A

24.0 Provisions to Protect the Privacy Interests of Subjects

24.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response: The study will be introduced to potential subjects in examination rooms with doors closed. Subjects who consent/assent to the study will provide authorization to access private health information that is to be collected for the study. All study testing will be done in a designated private and quiet area. Individuals not involved in the study will not observe the subject performing the indicated tasks.

24.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response: Potential subjects will be able to review the consent thoroughly and will be able to ask questions about the study prior to providing consent. The study tasks will be done in a designated private and quiet area.

24.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response: The study team has access to the electronic medical record (AllScripts EHR) in order to collect relevant data related to the study. All subjects will sign HIPAA authorization; except for the data collected from the study tasks, all other information is collected as part of standard of care during a diabetes clinic visit.

25.0 Compensation for Research-Related Injury

25.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response:

If you need medical care because of taking part in this research study, contact the investigator and medical care will be made available. Generally, this care will be billed to you, your insurance or other third party. The University at Buffalo and Kaleida Health has no program to pay for medical care for research-related injury.

25.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response: N/A

26.0 Economic Burden to Subjects

26.1 Describe any costs that subjects may be responsible for because of participation in the research.

Response: There are no costs associated with this research.

27.0 Consent Process

27.1 Indicate whether you will be obtaining consent

Response: Parental permission and/or consent will be obtained for all subjects.

27.2 Describe where the consent process take place

Response: The consent process will take place in the exam room in the outpatient UBMD Pediatrics Diabetes clinics at 1001 Main Street, 4th Floor Buffalo, NY.

27.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response: Some prospective subjects may decide to review the consent at home before deciding to participate. The period of time between introducing the study and obtaining consent could be as long as 3 months. Consent will only be obtained from individuals who are in agreement to the study.

27.4 Describe any process to ensure ongoing consent.

Response: Subjects will be asked at the beginning of Visit 2 and Visit 3 whether they are willing to continue with the study. In the unlikely event that an individual turns 18 years between the time of signing assent and performing study tasks, that individual will be reconsented and asked to sign the adult consent form.

27.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: SOP: Informed Consent Process for Research (HRP-090) will be used.

Non-English Speaking Subjects

27.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: The most common language other than English is Spanish.

27.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Response: Subjects who do not speak English will not be enrolled.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

27.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: N/A

27.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: N/A

Subjects who are not yet adults (infants, children, teenagers)

27.10 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized

Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response: We will use the date of birth to determine whether the individual has obtained legal age for consent. Any individual ≥18 years may provide consent. Assent will be obtained for all other subjects in addition to parental permission.

27.11For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: N/A

27.12Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: Permission will be obtained from one parent.

27.13Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response: Permission may be obtained by custodial guardians. We will require legal documentation prior to obtaining consent to permission for these individuals.

27.14Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response: All children age <18 years will provide assent.

27.15When assent of children is obtained describe whether and how it will be documented.

Response: Assent will be documented on a separate assent form which will be signed by the child. A copy of all documents will be provided to the family.

Cognitively Impaired Adults

27.16Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response: N/A

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

27.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

Response: N/A

27.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: N/A

27.19Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: Assent will be obtained from all subjects age 15 - <18 years. A separate assent form will be provided.

27.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: N/A

28.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

28.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response: We will be following HRP-091.

29.0 Drugs or Devices

29.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: The study drug will be obtained from the CTRC pharmacy prior to visit 2. The study drug will be given directly to the subject at the end of Visit 2. Subject will be advised that no other individuals may use the study drug. They will also be advised to bring the study drug with them for Visit 3. Study drug will be returned at the end of Visit 3 and will be disposed of by the principal investigator.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

29.2 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: IND exempt per FDA. See attached letter.

29.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: N/A