Title page:

Protocol Title: Functional sucrase deficiency in short bowel syndrome patients with intestinal failure

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1) **Protocol Title**

Functional sucrase deficiency in short bowel syndrome patients with intestinal failure

2) **Objectives**

Primary Aim:

To determine if sucrase supplementation in intestinal failure resulting from short gut syndrome will improve carbohydrate malabsorption, reducing symptoms such as bloating, diarrhea and abdominal pain and thus improve patient's ability to advance enteral nutrition in short gut syndrome patients.

Secondary aim:

To determine if reduced bowel mass/length that occurs in short gut syndrome results in decreased functional sucrase levels and thus disaccharide malabsorption causing symptoms such as bloating, diarrhea and abdominal pain and/or resulting in inability to advance enteral nutrition.

3) **Background**

Short gut syndrome patients have decreased production of disaccharidases, like sucrase, due to loss of enterocyte mass and thus these patients cannot digest sucrose fully.

The resulting maldigestion of sucrose causes abdominal distension, vomiting and diarrhea that limits the advancement of enteral nutrition in short gut syndrome patients with intestinal failure

The administration of exogenous sucrase will improve sucrose digestion and thus the advancement of enteral nutrition in short gut syndrome patients with intestinal failure.

Sucrose digestion:

Carbohydrates in the diet provide the major exogenous source for glucose, which is the primary energy source for cells. They account for 40-60% of the calories in the western diet and higher percentages in protein scarce diets.

Carbohydrates are hydrophilic and require a series of reactions to digest them to monosaccharides which are absorbed in the small intestine. The goal of carbohydrate digestion is to break down all disaccharides and complex carbohydrates into monosaccharides for absorption, although not all are completely absorbed in the small intestine - disaccharides are digested by specific enzymes, disaccharidases, in the microvillus membrane brush border. Disaccharidases are protected from proteolysis by glycosylation and are found in higher concentration in villus enterocytes of the proximal small bowel. The jejunum is the middle portion (mid-gut) of the small intestine and is where most nutrient absorption occurs. Some products of digestion that are not absorbed by the jejunum may also be absorbed by the ileum as this area can adapt to compensate for many of the jejunal functions.

Sucrase is the dissacharidase responsible for digestion of sucrose to fructose and glucose in the intestinal lumen. Sucrose uptake is then regulated after hydrolysis, by the apical membrane uptake rate of fructose and glucose. Carbohydrates not digested in the small intestine pass into the large intestine where they are digested by colonic bacteria. This results in the release of short chain fatty acids (SCFA) (propionate, butyrate and acetate) along with methane. The SCFA provide vital nutrition to colonocytes, but excess volumes induce diarrhea and abdominal cramping. Disaccharide deficiency results in symptoms due to an increased osmotic load in the small intestine and frequently elevated short chain fatty acid (SCFA) production in the colon.

Short Bowel syndrome:
Short bowel syndrome occurs most commonly following resections of the terminal ileum (such as in Crohn's disease or post-radiation enteritis), massive intestinal resection of infarcted bowel (due to compromised blood supply) and gastric bypass surgery as a therapy for weight loss. Common pediatric causes of short bowel syndrome include resections after episodes of necrotizing enterocolitis and repair of a volvulus. In rare cases, infants are born with a short bowel, congenital short bowel syndrome.

Intestinal failure is a subset of patients that are dependent on parenteral nutrition for some or all of their nutrition and fluid needs. Intestinal Failure is generally categorized as occurring secondary to (1) short bowel syndrome, referring to the spectrum of malabsorption that occurs after reduction of mucosal surface area from congenital or acquired lesions; (2) dysmotility or (3) mucosal enteropathy. These patients are unable to utilize enteral nutrients to meet the demands required for normal growth and development. Usually recurrent bouts of diarrhea, vomiting, abdominal distension and/or growth failure limit the advancement of enteral feeds. Deprivation of enteral calories, often termed “gut rest” in patients failing enteral nutrition, causes atrophy of the intestinal mucosa, even in the presence of adequate PN support. This may reduce the surface area of intestinal brush border and reduce the production of disaccharidases like sucrase and their release into the intestinal lumen for carbohydrate digestion.

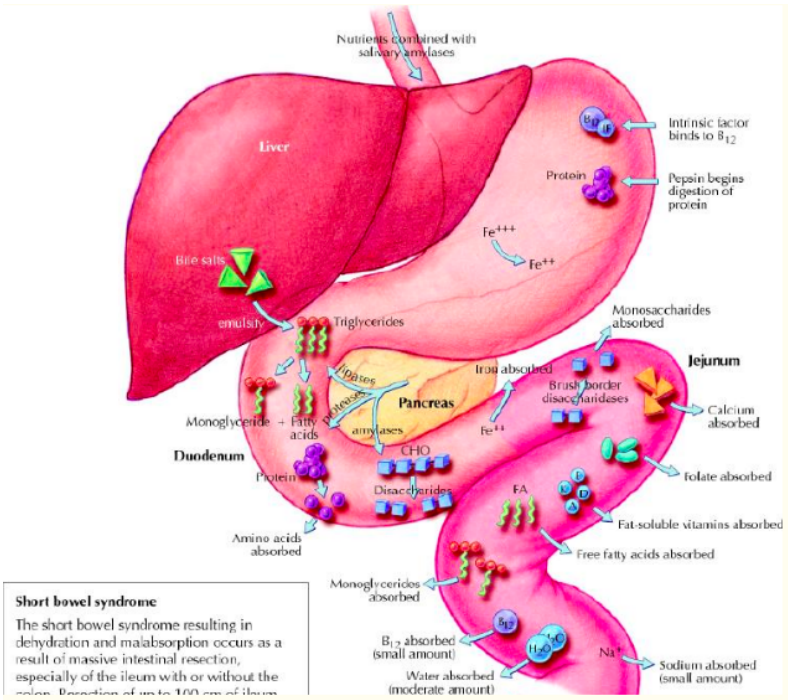


Figure 1: Intestinal digestion of macro and micronutrients

FORMULA	PROTEIN SOURCE	CARB SOURCE	FAT SOURCE
Similac Alimentum® (Abbott)	casein hydrolysate	sugar, modified tapioca starch	safflower oil, MCT, soy oil
EleCare® (Abbott)	amino acids	corn syrup solids	safflower oil, MCT, soy oil
Neocate Junior® (Nutricia)	amino acids	corn syrup solids	vegetable oil, canola oil, safflower oil
Splash® (Nutricia)	amino acids	maltodextrin, sugar	coconut oil, canola oil, sunflower oil
Peptamen Junior® (Nestle)	hydrolyzed whey protein	maltodextrin, sugar, cornstarch	MCT, soybean oil, canola oil

Table 1: SUCROSE IN FORMULA USED IN PEDIATRIC SHORT GUT SYNDROME

Short bowel syndrome has a reported 5-year mortality rate as high as 30%. The incidence of necrotizing enterocolitis (NEC) is increasing with increased survival of premature babies in neonatal intensive care units and it has been estimated that 12% of infants born weighing less than 1500g will develop NEC. Approximately 25% of NEC survivors have some degree of SBS. Updated medical management of these patients have improved survival in patients with SBS and at present, the 5-year survival rates from SBS in infancy and childhood range from 73% to 89%. Increasing incidence of SBS and improving 5-year survival rates leads to increase likelihood of physicians encountering these patients at some point in their practice. The most significant sources of morbidity and mortality in children with SBS are blood stream infections and parenteral nutrition-associated liver disease. Strategies that advance

enterally feeding thus eliminating need for parenteral nutrition and need for central venous catheters can significantly improve outcomes in short bowel population.

To my knowledge there have been no studies on disaccharidases in short bowel syndrome populations or the use of disaccharidase supplementation to improve carbohydrate digestion in these patients.

4) **Inclusion and Exclusion Criteria***

Inclusion:

- Short bowel syndrome, of all ages, with dependence on parental support to provide at least 50% of fluid or caloric needs.
- Must be on diet containing sucrose.
- Must be willing and able to sign informed consent
- Adult and Pediatric patients (all ages)

Exclusion:

- No current IV antibiotic administration for confirmed bout of bacteremia.
- Cannot be NPO
- Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results

5) **Study Design**

a) Overall Study Design (single arm, parallel, open label etc.)

Placebo controlled crossover trial.

b) Scientific rational for study design

Placebo-controlled design was chosen because when they are utilized with randomization, they allow for valid treatment group comparisons. The disadvantage of parallel designs is that they can require large sample sizes due to the existence of both within- and between-subject variation. Cross over studies generally require fewer participants than parallel designs because each participant serves as his/her own control, thus eliminating inter-participant variation. Secondly, researchers can study individual participant response to treatment and examine participant-by-treatment interactions. Lastly, study recruitment may

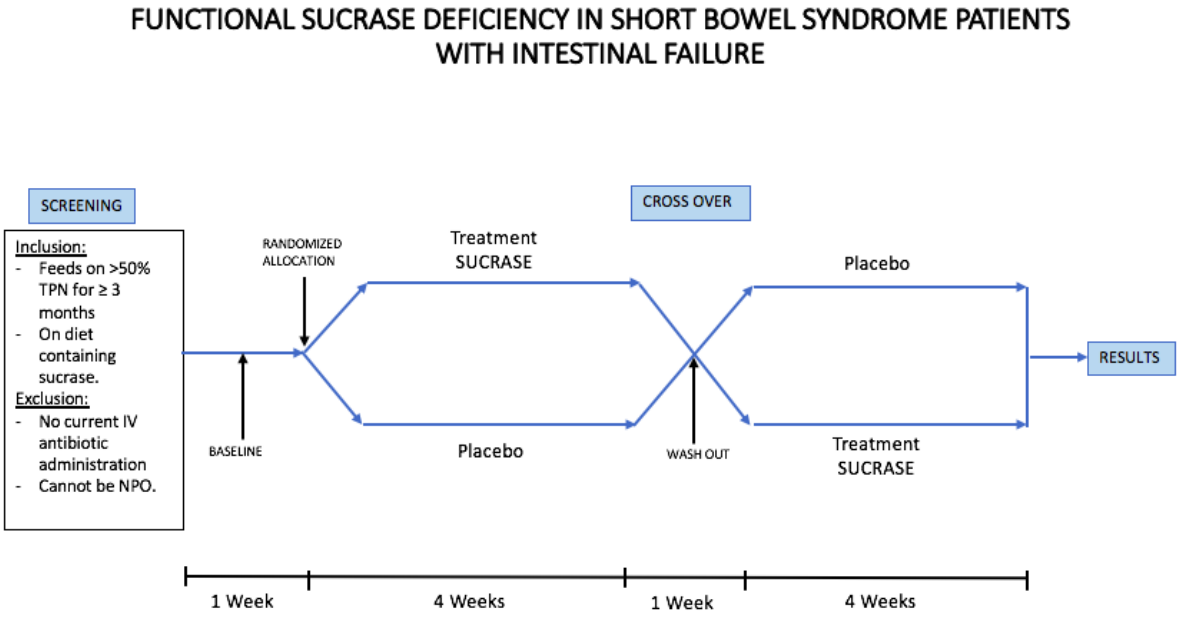
be enhanced as potential participants are aware that they will receive active treatment at some point during the study.

c) End of study definition

End of study will occur once all participants have undergone both intervention and placebo arm of the study. Each subject will be enrolled for study period of 9 weeks.

6) **Arms and Interventions**

Study Arm Description



Patients meeting inclusion criteria will be enrolled in the study and will provide written consented in keeping with regulations of the IRB.

Once enrolled "subjects" will be observed for 1 week on their current care and we will record:

Record daily:

Stool frequency and consistency

Side effects on sucrase – blood sugar checks by finger stick and any new symptoms – nausea, heacache, etc

Emesis

Record weekly:

Ability to advance feeds

Abdominal circumference

Weight

Patient or parent perception of tolerance of feeds on sucrase by telephone questionnaire

FUNCTIONAL SUCRASE DEFICIENCY IN SHORT BOWEL SYNDROME PATIENTS WITH INTESTINAL FAILURE

DAILY RECORD FOR EACH WEEK

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
STOOL FREQUENCY							
STOOL CONSISTENCY							
SUCRASE SIDE EFFECTS							
HEADACHE (YES/NO)							
NAUSEA (YES/NO)							
ABDOMINAL PAIN (YES/NO)							
VOMITING (YES/NO)							
BLOOD SUGAR							

WEEKLY RECORD (EXCEPT WASH OUT WEEK)

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
ABILITY TO ADVANCE FEEDS				
ABDOMINAL CIRCUNFERENCE				
WEIGHT				

	WEEK 6	WEEK 7	WEEK 8	WEEK 9
ABILITY TO ADVANCE FEEDS				
ABDOMINAL CIRCUNFERENCE				
WEIGHT				

FUNCTIONAL SUCRASE DEFICIENCY IN SHORT BOWEL SYNDROME PATIENTS WITH INTESTINAL FAILURE

TELEPHONE QUESTIONAIRE

	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 6	WEEK 7	WEEK 8	WEEK 9
Patient or parent perception of tolerance of feed on sucrase								

POSSIBLE ADITIONAL TESTING

- Blood test for genetic testing if available.
- If scheduled for an endoscopy, for other medically indicated reasons as decided by the medical team, will have biopsies taken to rule out CSID.
- Breath test for functional sucrase deficiency in patients who consent.

Study Intervention Description

Subjects will be administered sucraid (sucrase) daily as instructed and followed as above. There will be a one week wash out period

During cross over subjects will be administered “placebo” daily as instructed and followed as above.

a) Intervention dosing and administration information

The recommended dosage is as follows: 1 mL (8,500 I.U.) (one full measuring scoop or 28 drops) per meal or snack for patients up to 15 kg in body weight. 2 mL (17,000 I.U.) Dosage

is 1 or 2 mL (8,500 to 17,000 I.U.) taken orally or by g-tube with each meal or snack diluted in water, milk, or infant formula. Half of the dosage will be taken at the beginning of the meal or snack and the remainder be taken during the meal or snack. The beverage or infant formula should be served cold or at room temperature. The beverage or infant formula should not be warmed or heated before or after addition of Sucraid because heating is likely to decrease potency.

b) Study Intervention Compliance

Patients will be called weekly for verification of compliance. Most patients have home nursing so their home nursing records will be reviewed as well. Finally patients will be asked to verify how much medication they have left at end of each week to assess compliance.

7) **Procedures Involved**

Patients meeting inclusion criteria will be enrolled in the study and will provide written consented in keeping with regulations of the IRB.

Once enrolled "subjects" will be observed for 1 week on their current care and we will record:

Record daily:

Stool frequency and consistency

Side effects on sucrase – blood sugar checks by finger stick and any new symptoms –

nausea, headache, etc

Emesis

Record weekly:

Ability to advance feeds

Abdominal circumference

Weight

Patient or parent perception of tolerance of feeds on sucrase by telephone questionnaire

In the treatment arm of the study, subjects we will give sucrase at standard dose, 1 mL (8,500 I.U.) (one full measuring scoop or 28 drops) per meal or snack for patients up to 15 kg in body weight. 2 mL (17,000 I.U.), for a total of 4 weeks and follow patients recording stool frequency and consistency, emesis, weight, ability to advance enteral nutrition. Possible adverse effects of sucrase administration will also be recorded in addition to parental or patient perception of tolerance of feeds while on sucrase.

Give sucrase by g-tube or orally for 4 weeks
Record daily:

Stool frequency and consistency

Side effects on sucrase – blood sugar checks by finger stick and any new symptoms – nausea, headache, etc

Emesis

Record weekly:

Ability to advance feeds

Abdominal circumference

Weight

Patient or parent perception of tolerance of feeds on sucrase by telephone questionnaire

ONE WEEK WASH OUT – no recordings

Give placebo by g-tube or orally for 4 weeks
Record daily:

Stool frequency and consistency

Side effects on sucrase – blood sugar checks by finger stick and any new symptoms – nausea, heacache, etc

Emesis

Record weekly:

Ability to advance feeds

Abdominal circumference

Weight

Patient or parent perception of tolerance of feeds on sucrase by telephone questionnaire

Possible additional tests:
Some patients will undergo blood test for genetic testing if available, those who have been scheduled for an endoscopy, for other medically indicated reasons as decided by the medical team, will have biopsies taken to rule out CSID.
Patients who consent to breath test for functional sucrase deficiency will have testing done.

Procedures:

SucraidTM (sucrase) administration:
Subject will be asked to take sucrase either orally or through g-tube with feeds daily and will be provided with this medication at no cost. Subjects will take sucrase or placebo each for 4 weeks so they will be taking additional medication daily for 8 weeks as they participate in the study.

Sucrose breath test:
This is an optional test for children over 4 years old that can cooperate by drinking a solution containing sucrose (sugar water) and breathing into a device to record components of their breath. The test will be offered free of charge to subjects in the study. This test is performed at home and the kit can be mailed back to us. The mailing costs are pre-paid. Inability to perform breath test will not eliminate subject from the study.

Endoscopy:
Endoscopies are often performed to assess patients with short bowel syndrome with intestinal failure who are not progressing as expected. They are done to check for many things, such as, bacterial overgrowth in the intestine, inflammation in the intestine, loss of intestinal cell function, infections in the intestines etc. If a subject has had an endoscopy (obtained for clinical reasons), we will ONLY access these results for research purpose. If subject has not had an endoscopy one will only be performed if clinically indicated by medical team – we will not take additional biopsies or ask for additional tests at the time of endoscopy.

Telephone surveys:
We will conduct short telephone surveys of subject's symptoms while participating in the study. This would be similar to the phone calls they receive from the intestinal rehabilitation team about their feeds, stools, and other associated symptoms.

Medical chart review:
We will also look at recent growth chart in medical record to check growth before and during the study period, we will ask the parent or home nurse to measure abdominal circumference, weight and to check subject's blood sugars at home.

8) Outcome measures

Primary outcomes:

- Outcome Measure Title: Change in Carbohydrate Malabsorption
  Outcome Measure Description: Degree of carbohydrate malabsorption will be assessed by decrease in number of stools per day.
  Outcome Measure Timeframe: Baseline to Week 9
- Outcome Measure Title: Change in Carbohydrate Malabsorption
  Outcome Measure Description: Degree of carbohydrate malabsorption will be assessed by change in patient symptomatology by change in score on patient symptom survey.
  Outcome Measure Timeframe: Baseline to Week 9
- Outcome Measure Title: Change in Carbohydrate Malabsorption
  Outcome Measure Description: Carbohydrate malabsorption will be measured by increase in growth velocity in kg/week
  Outcome Measure Timeframe: Baseline to Week 9
- Outcome Measure Title: Change in Carbohydrate Malabsorption
  Outcome Measure Description: Carbohydrate malabsorption will be measured by ability to advance enteral nutrition in ml/day
  Outcome Measure Timeframe: Baseline to Week 9

Secondary outcomes

- Outcome Measure Title: Improved Digestion
  Outcome Measure Description: Improved digestion will be measured by decreased abdominal distension/girth measured in cm
  Outcome Measure Timeframe: Baseline to Week 9

- Outcome Measure Title: Improved Digestion
  Outcome Measure Description: Improved digestion will be assessed by number of emesis per day
  Outcome Measure Timeframe: Baseline to Week 9

- Outcome Measure Title: Improved Digestion
  Outcome Measure Description: Improved digestion will be assessed by change in stool consistency from hard to formed to semi solid to liquid with pieces to only liquid observed daily
  Outcome Measure Timeframe: Baseline to Week 9

9) **Adverse Events**

a) Definition of AEs

Reported adverse events are minor and rare with Sucraid (sucrase) and overdose has not been described. In clinical studies the adverse experiences were as follows: abdominal pain, vomiting, nausea, diarrhea, constipation, insomnia, headache, nervousness, and dehydration.

b) Definition of SAEs

In one study, one asthmatic child experienced a serious hypersensitivity reaction (wheezing) probably related to sacrosidase. The event resulted in withdrawal of the patient from the trial but resolved with no sequelae.

c) Time Period and Frequency for AE assessment and Follow-up

During weekly phone calls we will assess for worsening symptoms, including but not limited to the AE as listed above

d) Adverse Event Reporting

All adverse events as defined by the FDA will be recorded by study team and reported in the results section of the study and publications.

e) Serious Adverse Event Reporting

All adverse events as defined by the FDA will be recorded by study team and reported in the results section of the study and publications. Subjects will be withdrawn as necessary if SAE occurs during study period.

10) **Data and Specimen Banking**

Data will be kept on a secure drive and only be accessed by the study team members. Data will be de-identified prior to data entry.

Specimens taken for pathology (for other medically indicated reasons) will be kept in patients private medical record as usual.

11) **Data Management**

Statistics will be done in compliance with HIPAA regulations on de-identified data.

Data will be stored on a secure drive and only accessible to study team members during and after the study.

Data will be kept post collection in compliance with regulations.

12) **Risks to Subjects**

Sucrase may cause a serious allergic reaction.

Blood glucose levels may change after taking sucrase – each patient already has monitor to check daily sugars while on therapy.

Some patients treated with sucrase may have worse abdominal pain, vomiting, nausea, or diarrhea. Constipation, difficulty sleeping, headache, nervousness, and dehydration have also occurred in patients treated with sucrase.

Patients will only undergo endoscopy with biopsy if there is another medical indication as decided by the primary medical team (not the study team). Thus this risk does not pertain to the study.

13) **Potential Benefits to Subjects**

The most significant sources of morbidity and mortality in children with SBS are catheter related blood stream infections and parenteral nutrition-associated liver disease. Strategies that advance enterally feeding thus eliminating need for parenteral nutrition and thus central venous catheters can significantly improve outcomes in short bowel population.

14) **Participant Discontinuation/ Withdrawal from the study**

Participants may be discontinued if:

- They have bacteremia during course of study period and require IV antibiotic administration.
- They experience SAE or an AE that prevents them from continuing medication.
- They are admitted to the icu or hospital and made NPO during study period
- They undergo an unplanned surgery or procedure requiring them to be NPO for more than 12 hours
- They are switched by medical team to a diet not containing sucrose.
- They are no longer willing to participate in study

We will attempt to replace the withdrawn participant with another subject.
Any data collected on withdrawn subjects will be removed for purposes of statistical analysis.

15) **Vulnerable Populations**

NIL

16) **Setting**

Jackson Memorial Health system/University of Miami

17) **Resources Available**

Amanda Fifi, Assistant Professor of Pediatrics, Pediatric GI and Nutrition Specialist who runs the nutrition program at UM and Jackson that treats many patients with SBS. She has published articles on topic of SBS.

Jenn Garcia, Assistant Professor of Pediatrics, Pediatric GI and Short Bowel Syndrome Specialist who heads the Intestinal Rehabilitation and Intestinal Transplant service at Jackson and UM. She has published and presented data related to care of SBS for several years in many international meetings.

Miguel Saps, Professor of Pediatrics, Division Chief of Department of Pediatric GI, well-published, world-renowned Pediatric GI specialist and also prior consultant on use of sucrase in patients with sucrase deficiency.

18) **Prior Approvals**

NIL

19) **Recruitment Methods**

We will obtain approval through the institutional review board (IRB) at University of Miami and Jackson Health system. We will recruit patients, both adult and pediatric, through our Intestinal Rehabilitation Program at their regular clinic appointments in conjunction with the medical team. SGS is a rare disease and the list of patients with this condition that may meet criteria for this study is short. They will be approached in clinic by the primary medical team who follow these patients regularly. Patients will be consented in keeping with regulations of

the IRB. Only after recruitment and consent to participate in study will study access the medical records of the patients with their consent.

20) **Local Number of Subjects**

10 subjects

21) **Confidentiality**

Data, documents, reports, scans, specimens, etc. (not including consent documents) will be kept locally in a manner that is :

☐ Identifiable – provides least amount of protection

☒ De-identified and coded with the link between code and subject's identity maintained separately from the data.

☐ De-identified with no link to subject's identity

How will specimens obtained for this research be maintained?

☐ Identifiable – provides least amount of protection

☒ De-identified and coded with the link between code and subject's identity maintained separately from the data.

☐ De-identified with no link to subject's identity

If data or specimens will be coded, who will have access to the code sheet?

☒ Principal Investigator at UM/JHS

☐ Sponsor/funding entity

☐ Other, specify:

Data will be collected and stored on UM redcap and One Drive and will be password protected with password only known to specific members of the study team.
Paper Records (e.g., consent forms, data files, medical records, etc.): Paper files related to human subjects participation in research will be securely stored on campus. Access to files will be restricted to key personnel and supervised by the principal investigator(s) of the study. They will be kept in a secured office only accessible to PI.
Digital Records (e.g., electronic files etc.): Digital files containing human subjects research data will be stored in password protected files, on University maintained servers with regular and secured back-up. Sensitive data will also be encrypted, stored, and securely erased when appropriate.
Only the study team will have access to data.
Data will be de-identified and coded with the link between code and subject's identity maintained separately from the data prior to data entry and statistical analysis.
We will destroy or de-identify the information we collect at the earliest opportunity.
The information we collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

22) **Provisions to Protect the Privacy Interests of Subjects**

Data will be stored on a zip drive that is password protected with password only known to specific members of the study team.
Only the study team will have access to data
Data will be deidentified prior to data entry and statistical analysis

23) **Consent Process**

Written consent will be obtained for all subjects >18 years old involved in the study. One parent consent will be obtained for subjects <18 years old. Additionally subject assent will be obtained for subjects 10-17 years old.

24) **Process to Document Consent in Writing**

As above.

25) **References**

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