STUDY PROTOCOL

Salvage Peanut Oral Immunotherapy Study: A single-arm, open label trial of peanut flour with 6 month active treatment and 6 month follow-up

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Salvage Peanut Oral Immunotherapy Study: A single-arm, open label trial of peanut flour with 6 month active treatment and 6 month follow-up

PRINCIPAL INVESTIGATOR

Dr. Edwin Kim

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from Dr. Kim, unless it is necessary to obtain consent from potential study participants.

Version 3.0	Date: July 17, 2018
	Principal Investigator Dr. Edwin Kim
Short Title: Salvage peanut oral immunotherapy (SOIT)	

I have read protocol and I approve it. As the principal investigator, I agree to conduct this protocol according to Good Clinical Practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance" *(June 1996 (R1) and November 2016 (R2)), and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, state and federal requirements*

_____
Principal Investigator (Print)

_____ _____
Principal Investigator (Signature) Date

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SYNOPSIS

Title	Salvage Peanut Oral Immunotherapy Study: A single-arm, open label trial of peanut flour with 6 month active treatment and 6 month follow-up
Short Title	Salvage peanut oral immunotherapy (SOIT)
Clinical Phase	Phase II
Sponsor	Wesley Burks MD
Principal Investigator	Dr. Edwin Kim
Participating Site	The University of North Carolina at Chapel Hill
Accrual Period	2 years
Purpose	The primary purposes of the study are (1) to provide salvage therapy for individuals who previously participated in a peanut immunotherapy trial but did not demonstrate clinically significant desensitization, (2) to investigate the safety and tolerability of the salvage therapy regimen including both peanut flour and peanut flour equivalent, and (3) to explore mechanisms responsible for long-term desensitization and/or tolerance to food allergens induced by immunotherapy.
Study Design	This uncontrolled, observational, prospective, open-label study will be used to assess the safety and tolerability of a two-stage salvage therapy regimen: (a) peanut oral immunotherapy (OIT) followed by (b) extended maintenance with a peanut food equivalent.
Participants	We will enroll up to 100 eligible subjects who (1) did not demonstrate clinically significant desensitization in previous peanut immunotherapy trials, or (2) previously endured an extended time on placebo therapy, or (3) previously developed desensitization and then subsequently lost this protection due to time off from therapy.
Choice of Sample Size	The choice of sample size is based entirely on the ethical necessity of providing therapy to a pre-defined number of

	individuals in need of salvage therapy. We anticipate that up to 100 eligible subjects will be enrolled to receive the salvage therapy treatment regimen.
Study Duration	Approximately 12 months for each participant.
Primary Outcomes	• Overall incidence rate of adverse events (including both AEs and SAEs) during the entire 2-stage treatment sequence • Overall number of days of treatment missed during the entire 2-stage treatment sequence
Secondary Outcomes	• Stage-specific incidence rate of all adverse events • Days of treatment missed during each stage of treatment. • Overall incidence rate of gastrointestinal AEs during the entire 2-stage treatment sequence. • Overall incidence rate of Epipen use • Overall incidence rate of drop-outs due to gastrointestinal AEs during the entire 2-stage treatment sequence.
Exploratory Measures	• Changes in basophil, T cell, and antibody responses in peripheral blood and saliva samples (to explore the mechanisms responsible for long-term desensitization and/or tolerance to food allergens induced by immunotherapy.)
Inclusion Criteria	• Subjects who have completed an immunotherapy trial for peanut allergy within the last 18 months and are unable to tolerate ≥ 300mg of peanut. • Age 1-65 years of either sex, any race, any ethnicity. • Written informed consent from patient or parent/guardian (if < 18 years) with participant's assent.
Exclusion Criteria	• Current participation in an interventional study for peanut allergy • History of a severe anaphylactic reaction to peanut, defined as hypoxia, hypotension, or neurologic compromise (cyanosis or SpO2 < 92% at any stage, hypotension, confusion, collapse, loss of consciousness, or incontinence)

	• Eosinophilic or other inflammatory (e.g. celiac) gastrointestinal disease • Severe asthma (2007 NHLBI Criteria Steps 5 or 6 – Appendix 2) • Use of □-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers • Significant medical condition (e.g., liver, kidney, gastrointestinal, cardiovascular, hematologic, or pulmonary disease) which would put the subject at risk for induction of severe food reactions. • Pregnancy or lactation.
Study Procedures	The following procedures will be performed: • Medical and allergy history (including dietary history) • Physical examination • Peak flow rates (if capable) • Oral immunotherapy (OIT) • Serum analysis for peanut-specific immunoglobulins (ImmunoCAP) (optional) • Peanut skin prick testing (optional) • Saliva collection (optional) • Pregnancy test for females in childbearing age.

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CTCAE	Common Toxicity Criteria Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTRC	Clinical Translational Research Center
DBPCFC	Double Blind Placebo Controlled Food Challenge
DSMB	Data Safety Monitoring Board
FASC	Food Allergy Study Center
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRQL	Health-Related Quality of Life
ICH	International Conference on Harmonization
IND	InvestigationalNew Drug
IRB	Institutional Review Board
NIAID	National Institute of Allergy and Infectious Diseases
OFC	Oral Food Challenge
OIT	Oral Immunotherapy
PI	Principal Investigator
SAE	Serious Adverse Event
SPT	Skin Prick Test
SU	Sustained Unresponsiveness
UNC	The University of North Carolina at Chapel Hill

1. BACKGROUND AND RATIONALE

A. BACKGROUND

Food allergy is a significant public health problem that is increasing in prevalence. According to recent CDC data, approximately 4% of children are affected by food allergy while 1.3% of the total population is allergic to peanut or tree nuts. Despite recent increased recognition and understanding of the disease, food allergy is the most common cause of outpatient anaphylaxis, and peanut allergy is the most common cause of fatal anaphylaxis. In the United States, it is estimated that emergency departments treat about 30,000 food-induced anaphylactic events each year, and that about 200 fatal cases occur annually.

Currently the only available preventative treatment for food allergy is strict avoidance of the allergenic food. Food avoidance involves a lifestyle change for families, requiring careful reading of food labels, exercising caution when dining at restaurants, and carrying rescue medications at all times. For these reasons, food allergy is known to significantly impact the quality of life for both patients and their families. These findings stress the importance of developing improved therapies for food allergy.

B. RATIONALE

An increasing number of studies have proved the concept that peanut immunotherapy can desensitize subjects with peanut allergy by regulating their mucosal and systemic immune reactivity. This has culminated in the development of a large phase 3 study of peanut OIT that is currently underway with guidance from the US Food and Drug Administration (FDA). However, there are important aspects of peanut OIT that remain to be studied and are the subject of more recent studies. These include questions about the durability of the desensitization effect termed sustained unresponsiveness (SU), the effect of peanut OIT in special populations such as very young children, and the prevalence of certain side effects such as eosinophilic esophagitis. With this gradual shift away from equipoise, a need

for providing a salvage therapy option for those who continue to volunteer to participate in research studies has become apparent. Two populations of particular interest are those who have previously developed desensitization and then subsequently lost this protection and those who have been randomized to extended courses of placebo drug.

In many current studies of peanut OIT, subjects are initially desensitized and then subsequently asked to avoid peanut for a discrete amount of time in order to assess the durability of the desensitization effect (sustained unresponsiveness). This research is critical to understanding the clinical and immunologic changes induced by peanut OIT and longer term implications of therapy. However, in the course of these investigations, the potential exists for subjects to lose their desensitization to peanut and their protection against accidental exposures to peanut.

The majority of current studies of OIT utilize a placebo group, some for extended periods of time (> 1 year). These extended placebo courses are vital to understanding the efficacy of OIT as up to 20% of peanut-allergic patients are thought to naturally develop tolerance to peanut. These subjects are not thought to be at any higher risk than those who are strictly avoiding peanut which is the current standard of care. However, concerns remain with withholding potentially protective treatment for these extended periods of time.

The use of investigational drugs to induce and maintain desensitization has been and continues to be the subject of numerous ongoing studies. However, there has been growing interest in the use of food products to maintain this effect with the thought that these readily available foods may allow for superior compliance. The safety and compliance with transitioning to a non-drug equivalent amount of peanut food has not been well studied.

The goals of this study protocol are several-fold. First and foremost, we would like to provide a salvage therapy option for those previously involved in vital peanut allergy research. Simultaneously, we will address three research aims:

Aim 1 --Investigate the safety and compliance in the 2-stage protocol in subjects who either (a) have previously developed desensitization and then subsequently lost this protection due to a period of time off of therapy or (b) have previously endured an extended time on placebo therapy.

Aim 2 -- Characterize and compare the two stages of the protocol in terms of safety and compliance.

Aim 3 -- Explore the mechanisms responsible for long-term desensitization and/or tolerance to food allergens induced by immunotherapy.

In doing this, we aim to add to the accumulating pool of data on the safety of OIT while providing a salvage option for these subjects. The data generated from our study can guide future research to identify high risk groups for peanut oral immunotherapy, and compare safety and compliance between peanut OIT and peanut food equivalents. A food equivalent of peanut containing food is an available food in the market with known doses of peanut protein (e.g. Reese's peanut butter cups, Peanut M&Ms, etc.)

2. POTENTIAL RISKS AND BENEFITS

A. RISKS

The main risks for participating in this study include:

1. Allergic symptoms during the initial escalation, build up or maintenance phase: including sneezing, rhinorrhea, urticaria, angioedema, flushing, eczema flare, nausea, vomiting, diarrhea, abdominal discomfort, cough, wheezing, dyspnea, pruritus (ocular, nasal, oral, throat) or anaphylaxis.
2. Skin prick testing (SPT) is an optional procedure in the study and may result in a small, pruritic hive where the test is placed. Usually, the hives resolve within 1-2 hours, but rarely a subject may have local swelling that takes two to three days to clear entirely. Very rarely, some individuals may develop a serious allergic reaction that is life threatening, but no deaths from prick skin testing using standard dosing techniques have been reported in fifty years. Skin prick testing will be supervised by a physician or nurse coordinator, and rescue medications will be readily available if any reaction occurs.
3. Blood draws for mechanistic studies are an optional procedure in the study and result in pain and discomfort, bleeding, bruising where the needle is placed, and, in rare cases, fainting and infection. In order to minimize the risk of anemia, the maximum volume of blood to be drawn will be less than 2 ml/kg of body weight per visit up to a maximum of 45 ml in 8-week period for pediatrics and less than 550 ml in an 8-week

period for adults. This maximum amount applies for both clinical or research purposes: clinical blood draw will be considered prior to research blood draw). Blood collection will not occur more than 2 times per week.

B. Benefits

The benefits from this study include:

1. The potential of decreasing the participants' reactivity to peanut after an accidental ingestion by developing desensitization to at least an equivalent of the daily tolerated maintenance dose (300 mg of peanut protein). Most accidental exposures to peanut protein are believed to be less than 200 mg. (Schäppi, GF et al. 2001).

2. This study will expand the general knowledge of food allergy. This applies specifically to safety of peanut oral immunotherapy and identifying high risk groups. This may lead to new management and therapeutic protocols for individuals with peanut allergy, or food allergy in general.

3. OBJECTIVES AND OUTCOME MEASURES

A. Objectives

1. The primary objective of this study is to place patients who have been involved in peanut immunotherapy research on salvage therapy while investigating safety and compliance of oral immunotherapy and food equivalent therapy in these patients.

2. The secondary objectives include:
   a. Investigation of incidence of gastrointestinal adverse event, drop outs, and Epipen use.
   b. Investigation of the compliance of participation with peanut OIT and peanut food equivalent

B. Outcome Measures

1. Primary Outcomes

- Overall incidence rate of adverse events (including both AEs and SAEs)

during the entire 2-stage treatment sequence (OIT followed by peanut containing food equivalent)

- Overall number of days of treatment missed during the entire 2-stage treatment sequence

2. Secondary Outcomes

- Stage-specific incidence rate of all adverse events
- Days of treatment missed during each stage of treatment.
- Overall incidence rate of gastrointestinal AEs during the entire 2-stage treatment sequence.
- Overall incidence rate of Epipen use
- Overall incidence rate of drop-outs due to gastrointestinal AEs during the entire 2-stage treatment sequence.

4.SELECTION AND WITHDRAWAL OF PARTICIPANTS

A. INCLUSION CRITERIA

Anyone meeting all of these criteria is eligible for enrollment as study participants:

1. Age 1-65 years of either sex, any race, any ethnicity.
2. Subjects who have completed an immunotherapy trial for peanut allergy within the last 18 months and are unable to tolerate ≥300mg of peanut.
3. Written informed consent from patient (if ≥ 18 years) or permission of parent/guardian with participant's assent (if between 7-17)

B. EXCLUSION CRITERIA

Participants who meet any of these criteria are not eligible for enrollment as study participants:

1. History of a severe anaphylactic reaction to peanut, defined as hypoxia, hypotension, or neurologic compromise (cyanosis or SpO2 < 92% at

any stage, hypotension, confusion, collapse, loss of consciousness, or incontinence)

2. Eosinophilic or other inflammatory (e.g. celiac) gastrointestinal disease
3. Severe asthma (2007 NHLBI Criteria Steps 5 or 6 – Appendix 2)
4. Use of β-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers
5. Significant medical condition (e.g., liver, kidney, gastrointestinal, cardiovascular, hematologic, or pulmonary disease) which would put the subject at risk for induction of severe food reactions.
6. Currently participation in an interventional study for peanut allergy.
7. Pregnancy or lactation.

C. Premature Withdrawal Criteria

Participants may be prematurely withdrawn from the study if:

1. At any point in the study, the participant elects to withdraw consent from all future study activities.

2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).

3. The participant develops a medical condition that the investigator deems incompatible with participation in the trial. That includes specifically developing Eosinophilic Esophagitis (participants who develop symptoms compatible with Eosinophilic Esophagitis will be referred to a gastroenterologist).

4. Severe atopic dermatitis requiring oral steroids or immunmodulatory agent, or severe asthma; requiring more than daily medium dose inhaled corticosteroids (more than Flovent 440 mcg daily or its equivalent)

5. The use of systemic corticosteroids in the past 30 days.

6. The participant experiences severe symptoms during the build-up or maintenance phases as a result peanut OIT dosing

7. In the investigator's discretion, there is poor compliance or any other concern that would create an unacceptable risk to the subject.

8. The participant dies.

9. The study ends.

To the extent possible, participants who discontinue therapy will be followed to observe and record study outcomes.

D. Study termination criteria

If any of the stopping rules listed below are met, study enrollment will be suspended, the initial dose escalation phase and build-up phase will be stopped, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data by the Data Safety Monitoring Board:

1. Any death related to peanut OIT dosing.

2. More than one event comprising systemic allergic symptoms with significant hypotension at any stage of the protocol.

3. More than 3 participants require more than 2 injections of epinephrine during dosing of the peanut product.

4. More than 3 of the following events:

- Severe adverse event, other than anaphylaxis, related to investigational product.
- Eosinophilic esophagitis.

5.STUDY DESIGN AND SCHDULE

A. Location

Visits will be done at the University of North Carolina-Chapel Hill Food Allergy Study Center (FASC), located in the CTRC building. The FASC is equipped as a clinic. In addition to MD and NP coverage, there are 24-hour adult and pediatric rapid response teams in case of emergencies. The study

site is adjacent to the UNC Hospitals Emergency Department where subjects can be transferred for continued monitoring and acute care as needed.

B. Duration of enrollment

The study enrollment duration is for 2 years or until a commercial peanut OIT products is available to participants whichever is sooner.

C. Duration of the study per participant

Each participant will be in the study for a total of 12 months. There will be three phases in the study: escalation phase for 1 day, build up phase up to 16 weeks, and maintenance phase up to 3 months on peanut OIT followed by 6 months of food equivalent to tolerated peanut protein.

D. Study visits

Participants will have: an initial study visit (screening), followed by one visit for the escalation phase, followed by visits every 1-2 weeks for the up dosing phase, a visit at the end of peanut OIT treatment at 6 months, a phone interview at 9 months and a final visit at the end of the study at 12 months. The screening visit may be combined with the initial escalation visit.

1. Screening and baseline visit

We will perform screening during the initial study visit. We will determine if the patient is still eligible for the study, discuss the study and consent with the patient, perform physical exam and spirometry (participants ≥ 7 years old). A blood draw and skin prick test may also be performed.

2. Escalation phase

All subjects will undergo a one-day peanut desensitization protocol to enable them to tolerate a daily dose of peanut protein (3-6 mg) (Table I). If the participant has a reaction to one of the doses in the escalation, the next dose will be determined at the discretion of the investigator. The options open to the investigator are to administer the last previously tolerated dose, or wait an additional amount of time between doses. Once this determination of the dosage amount is made, the desensitization process resumes as outlined.

Upon completion of the modified escalation phase to peanut, the subject is observed for a minimum of 2 hours. If there is no evidence of an allergic reaction the subject is discharged home. If the subject requires treatment for symptoms during the initial escalation protocol with antihistamines on one occasion, then the rest of the protocol may be followed. If the subject requires more than one medication or multiple doses of antihistamines or requires other rescue medications, the initial desensitization phase should be stopped. If the subject has tolerated either the 3 mg or 6mg dose, the subject will be eligible to return on Day 2 to proceed with the build-up phase Subjects must be able to tolerate the first two doses of escalation with mild or no symptoms to continue with build-up.

Table I

Dose #	**Dose**	**Interval (minutes)**	**% Increase**
1	**1.5mg**	**30**	**100**
2	**1.5mg**	**30**	**0**
3	**3mg**	**30**	**100**
4	**6mg**	**30**	**100**

3. BUILD UP PHASE

After the first day of desensitization, subjects will return to the research unit the following day to begin the build-up phase of the study. The subject will ingest 6 mg, or a lower amount based on the reaction during the escalation phase. After the subject is observed for a minimum of 30 minutes for symptoms to the study protein ingestion, he or she will be discharged from the research unit and will continue to consume the study protein at home daily fourteen days (-3/+7 days). The family receives the study protein doses as a powder that they give to the child each day by sprinkling it on a previously tolerated food (e.g., apple sauce). Subsequently, subjects will return to the clinical research unit every 2 weeks (-3/+7 days) to monitor their adherence to the dosage administration and increase the dose to the next escalation amount (Table II). Vital signs are performed prior to the dose administration, prior to the completion of the observation period before discharge, and anytime symptoms occur. If the study team feels that a longer observation time is warranted based on the prior dosing history of the subject or their current physical status, the subject will be observed for a longer period of time. If symptoms occur that do not require treatment, the subject will

be observed until they resolve. If symptoms occur that require diphenhydramine or albuterol, the subject will be observed a minimum of 2 hours or until symptoms resolve. If symptoms occur that require epinephrine, the subject will be observed at least 4 hours or until symptoms resolve. If symptoms do not fully resolve after 6 hours or if new symptoms occur, the subject will be transferred to UNC Children's Hospital to be observed overnight. Per individual stopping rules, participants experiencing severe symptoms during buildup will be terminated from the study.

Subjects who tolerate dose escalations will take that dose daily for a period 2 weeks (-3/+7 days) after which they will return to the clinical research unit to have the daily dose increased proportionately at each visit until the maximum daily dose of study protein (300 mg) is reached. Mechanistic studies may be done at the discretion of investigator to address any clinical symptoms for further studies.

Table II

Dose #	**Dose**	**Interval(weeks)**
5	**6mg**	**Day 2**
6	**12mg**	**2**
7	**25mg**	**2**
8	**50mg**	**2**
9	**75mg**	**2**
10	**100mg**	**2**
11	**150mg**	**2**
12	**225mg**	**2**
13	**300mg**	**2**

4. MAINTENANCE PHASE

After completing build up phase to 300 mg study protein, the subjects will continue to receive their maintenance dose of study protein daily for the proceeding 3 months of the study (maintenance phase). After 3 months of maintenance, the subject may have mechanistic studies done at end of study visit. Data from our previous studies indicate that home dosing is safe, with infrequent

reactions which are typically mild. These data have identified several risk factors for reactions, which include dosing on an empty stomach, fever/illness, and activity/exercise shortly before or after dosing. Families of subjects will be asked to administer the study protein with additional food such as at snack or meal times, and will be instructed to hold the dose during illness and contact study personnel for instruction. After 3 months of daily maintenance peanut protein OIT, subjects will have a follow up visit where they are assessed by study investigator and if qualified they will be switched to food equivalent of peanut protein for the following 6 months.

5. Peanut food equivalent phase

At the end of maintenance peanut OIT phase, subjects will be given instruction during their last study visit in maintenance phase to start a peanut food equivalent of 300 mg peanut protein: which include the following options: peanuts (not dry roasted), peanut butter, powdered peanut butter, mini snickers, mini Reese's cup, cheese peanut butter crackers, Reese's pieces, Reese's peanut butter chips or Goober. An instruction sheet will be provided on how much to take of one of these products on a daily basis This phase will last for 6 months. During this phase, subjects will continue to fill compliance sheets and they will receive phone calls from study coordinators at 9 months. This will be no study visits until the end of this phase to hand daily compliance sheets and fill a survey. At the end of the study the subjects may have the option to enroll in our peanut OIT follow up study if study investigator deemed they meet inclusion criteria for the study.

E. Handling adverse reactions and follow up during home dosing

Each subject is given multiple ways to contact study staff when they are enrolled in the study. This is reviewed at the end of each visit. The families are told to contact the study staff if they have any questions or concerns before the next visit or at any time during the study. Study contact information given to families include the research clinic phone number, email addresses and office numbers of the, study coordinators, and instructions for how to get in contact with the pediatric on-call allergist who can reach the lead coordinator if needed. Subjects who have any symptoms during observed dosing, or those who express any specific concerns are given a follow up phone call on the day after dose escalation. All subjects will be asked to carry an auto-injector epinephrine. If prescription is not provided by their physician, we will provide them with a prescription for an auto-injector epinephrine. We will ask subjects to fill their prescription and

bring their epinephrine auto-injector with them before starting treatment to verify they have filled their prescription.

F. Managing missed doses

Subjects who miss one to two days of the daily dose will continue at their current dose at home. The PI will determine where the next dose of study protein is given for those who miss three to four days of the daily dose based on the length of time on study, the daily dose amount, the subject's reaction history and the amount of time since the last reaction to a dose in order to assure safety with dosing. Those who miss more than four consecutive days will return to the clinical research unit for evaluation by the study team in order to determine the best course of action for the subject. Options open to the investigator include repeat desensitization, observed dosing at the current level, or observed dosing at a dosing level previously tolerated by the subject. All such management of missed doses will be carefully documented in the study database.

G. Monitoring of side-effects, adverse events, and clinical changes

- We will monitor accidental reactions to peanuts in each subject during each visit to the study center. We will note any reaction that occurs in a subject within two hours after the ingestion of peanuts, and record the type of symptoms (i.e., skin, respiratory, gastrointestinal, or cardiovascular). A copy of the CRF is in the appendix.
- To monitor subjects for adherence, any accidental ingestion, any symptoms related to daily dosing and any unintended side-effects of daily dosing, the families will be asked to keep a simple daily diary to record the requested information. A copy of the daily diary is included in the appendix of the protocol.
- We will check mechanistic changes in the immune system by checking lab tests, skin testing or spirometry during the study.

6. STUDY PROCEDURES

A. History taking, physical exam and peanut oral immunotherapy administration

Please refer to 5.e for detailed description of study visits. In each study visit medical and allergy history will be reviewed (including dietary history) and physical exam will be performed before administering any treatment. Peanut OIT will be administered according to schedule provided in Table I and II.

B. Skin Prick Testing (optional)

Participants will have standard allergen skin prick tests (SPT) performed to peanut and possible other allergens based upon the subject's history and at the discretion of the investigator. The investigator will document in the database the rationale for performing the optional SPT. Examples include: checking mechanistic studies for subjects who develop specific gastrointestinal side effects (e.g. EoE), subjects who are unable to tolerate desensitization to 300 mg or subjects with severe adverse events.

If skin prick testing is schedule for a certain visit, the participant will be notified prior leaving appropriate length of time to stop any antihistamines at the discretion of the investigator (5 half-lives of the antihistamine that is being used). A skin test probe is loaded with extract (Greer) then used to prick the epidermis. Positive (histamine) and negative (saline-glycerine) controls are placed as well to establish that the response is not blocked and to determine if there is dermotagraphism, respectively. The tests are read 15 minutes after placement, outlined in pen for wheal and flare and transferred by cellophane tape to paper to establish a record. SPTs are considered positive if there is a mean wheal diameter of 3 mm or greater, after subtraction of the saline control. Histamine wheals should be 3mm larger than the saline, and any saline wheel measuring larger than 3mm would invalidate the test and should be repeated.

C. Blood draw:

Venous blood may be obtained during the study for serum based assays (including but confined to serum peanut specific IgE). Blood drawn will be less than 2 ml/kg of body weight per visit up to a maximum of 45 ml in 8-week period for pediatrics and less than 550 ml in an 8-week period for adults. Blood collection will not occur more than 2 times per week.

D. Spirometry

Spirometry will be done for every subject 7 years or older in screening visit.

Afterwards, if clinical indicated, spirometry will be administered per clinic asthma standard of care as an assessment of lung function in subjects 7 years of age or older during study visits. Procedures follow American Thoracic Society criteria. Bronchodilation is not conducted and beta-agonists do not need to be withheld prior to the test. The test is administered while the subject is in a standing position and using a nose clip. We will reference the Hankinson predictive values for lung function. Subjects between 7 and 11 years who are unable to perform spirometry will be offered an attempt to use a peak flow meter. Participants who are unable to maintain >80% PEFR of their predicted value will need to be evaluated by the NP or MD before proceeding.

E. Saliva collection (optional-subject to the investigator discretion)

A 0.5 ml of saliva could be collected to run mechanistic assays as determined by the investigator. Examples include: checking mechanistic studies for subjects who develop specific gastrointestinal side effects (e.g. EoE), subjects who are unable to tolerate desensitization to 300 mg or subjects with severe adverse events.

Samples may be obtained by the subject spitting independently or the coordinator using a plastic syringe to gather saliva.

F. Compliance sheets

Subjects will be given sheets to record their compliance with the medication that needs to be changed on a weekly basis. The sheets will also include reactions the subjects have, the symptoms they experienced and how they were treated. Subjects will hand the sheets to their study coordinator at each visit and at the end of the study. The data from these sheets will be used to assess compliance and adverse events in addition to information gathered from subjects from their follow up surveys.

G. Urine pregnancy test

All participating females of child bearing age will have pregnancy urine test in screening then for the last follow up visit within 30 days of the last pregnancy test. Female subjects who become pregnant will be taken out of the study. Sexual abstinence will be accepted as an effective method of

contraception.

Sexually active female subjects are to use either:

- A highly effective method of birth control, defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner; or

- Alternatively, if a highly effective method of birth control is not used, an effective, double barrier method of contraception (e.g., male condom with female condom, cervical cap, diaphragm, or contraceptive sponge) may be used.

7. Study agent

A. Formulation, packaging and labeling

Peanut flour will be packaged and labeled by the weight (mg) of the source material in each cup per dose at the University of North Carolina GMP manufacturing facility. Both the investigational drug as well as placebo (oat flour) are manufactured as described in Master File Type II MF2 15171.

B. Preparation, administration and dosage

The investigational pharmacist will dispense the appropriate dose to the clinical staff. The peanut flour will be mixed into a food vehicle (applesauce, yogurt, or other tolerated food) for the subject to consume

C. Starting dose and escalation schedule

Please refer to 5.E.

D. Dose adjustment

Please refer to 5.E, 5.F. and 5.G.

E. Duration of therapy

Total duration of therapy with peanut flour will be up to 6 months. This will be followed by 6 months of peanut equivalent.

F. Rescue medication and concomitant medication

Treatment of individual allergic reactions during OIT therapy will be with either an antihistamine and/or epinephrine, along with IV fluids, albuterol, and corticosteroids as indicated. Participants and parents are likely to have self-injectable epinephrine but for those who do not, self-injectable epinephrine will be prescribed in clinic. Participants will be trained in proper use of self-injectable epinephrine and will be able to demonstrate proper technique. All subjects will be given a food allergy action plan to follow while in this study.

8. SAFETY MONITORING

A. Definitions

Adverse Event (AE) or Medical Event

An adverse event is a new, undesirable medical event or occurrence or worsening of an existing condition (including an abnormal laboratory finding) in a subject that occurs during the study, whether or not it is considered to be study related. Adverse events or medical events and toxicities are treatment emergent signs and symptoms.

Serious Adverse Event (SAE)

A serious adverse event is defined as any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but may not be limited to any of the following events: (This terminology is from Section B.2 on the FDA MedWatch form. For a copy of the current MedWatch Form 3500, see the list of PDF forms on the Web at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html)

1) Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-

up after the completion of therapy whether or not considered treatment-related, must be reported.

2) Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death)

3) In-patient hospitalizations.

4) Persistent or significant disability or incapacity.

5) Congenital anomaly/birth defect.

6) An event that required intervention to prevent permanent impairment or damage

Unexpected Adverse Events

An adverse event is considered "unexpected" when its nature or severity is not consistent with the descriptions in the protocol or informed consents.

For subjects who become pregnant during the study and whom we will withdraw from the study as stated above, we will continue to monitor them with phone calls every 3 months until delivery. We will use our phone interview questionnaire to report any adverse outcomes for these subjects and report the outcome of all pregnancies in our study report.

B. Toxicity Grading

Symptoms associated with systemic allergic reactions and/or anaphylaxis that occur during administration of peanut flour or peanut equivalent food will be graded according to table below, that was adapted from the grading of allergic reactions in the following article:

Burks A, Jones S, Wood R, *et al*. 2012. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. Table 1 (Suppl): 367:233–43

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening	Grade 5 Death
Transient or mild discomforts (< 48 hours), no or minimal medical	Symptoms that produce mild to moderate limitation in activity some assistance may be needed; no or	Marked limitation in activity, some assistance usually required; medical intervention/therapy	Extreme limitation in activity, significant assistance required; significant	Death

intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting or other symptoms	required, hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated.	medical/therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.	

Other adverse events related to study procedures other than peanut flour or peanut equivalent and adverse events that are not associated with study procedures will be graded according to the criteria in the National Cancer Institute NCI –CTC, as following:

Grade 1 Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2 Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3 Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4 Life-threatening	Extreme limitation in activity, significant assistance required; significant

	medical/therapy intervention required, hospitalization or hospice care probable.
Grade 5Death	Death.

<u>Anaphylaxis:</u>

Anaphylaxis will be defined according to second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium (Sampson H, Muñoz-Furlong A, Campbell R, *et al*. 2006. Second symposium on the definition and management of anaphylaxis: Summary report: Second NationalInstituteof AllergyandInfectiousDiseases/FoodAllergyand AnaphylaxisNetworksymposium.*J AllergyClinImmunol*.92:397–403) as following:

Table I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure **TO A <u>LIKELY</u> ALLERGEN FOR THAT PATIENT** (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to **KNOWN ALLERGEN FOR THAT PATIENT** (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; **BP**, blood pressure.

* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Eosinophilic Esophagitis:

We will monitor subjects for the development of eosinophilic esophagitis using Modified Aceves Questionnaire for all of our patients. The questionnaire will be done at screening, then visits 4,6,9,10,11 and 12. The answers in the questionnaire will be scored and those who have a score of 5 or more will be evaluated for possible Eosinophilic Esophagitis and will be referred to gastroenterology

C. Relationships to Procedure Definitions

Associated: There is a reasonable possibility that the adverse event may have been caused by the test product and/or procedure. This definition applies to those adverse events that are considered definitely, probably or possibly related to the procedure.

1) **Definitely related:** An adverse event that follows a temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test article and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test product (and by

reappearance of the reaction after repeat exposure); and cannot be reasonably explained by known characteristics of the subject's clinical state or by other therapies.

2) **Probably related:** An adverse event that follows a reasonable temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test product and/or procedure, is confirmed by improvement after stopping administration of the test product or stopping the procedure; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.

3) **Possibly related:** An adverse event that follows a reasonable temporal; sequence from administration of the test product and/or procedure and follows a known response pattern to the test product and/or procedure, but could have been produced by the participants' clinical state or by other therapies.

Not associated: An adverse event for which sufficient information exists to indicate that the etiology is not related to the test product and/or therapy.

Unrelated: An adverse event that does not follow a reasonable temporal sequence after administration of the test product and/or procedure; and most likely is explained by the participant's clinical disease state or by other therapies. In addition, no change in a reaction with stopping or restarting the test product or procedure would support an unrelated relationship.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI- CTCAE website, http://ctep.cancer.gov/reporting/ctc.html.

D. Adverse Events Collection Procedures

The Principal Investigator is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified and reported as described above. The Principal Investigator will determine relationship of the event to the study activities and decide the course of action for the study participant.

Adverse events will be evaluated from the onset of the event until the time the event is resolved or medically stable or until 30 days after reporting of the event, whichever comes first.

Adverse events may be discovered through any of these methods:

1. Observing or questioning the participant during study visits.

2. Reviewing the forms given to the patient for home monitoring and documenting compliance.

3. Receiving an unsolicited complaint from the participant.

E. Serious Adverse Event Notification

The research staff will notify the principle investigator of any serious adverse event immediately on learning about the event. Serious adverse events will be recorded on the adverse event CRF within 24 hours of their occurrence. The following attributes must be assigned:

- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to test procedure
- Action taken

The principal investigator must apply their clinical judgment to determine whether an adverse event is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator must suspend any trial procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

Subsequent review by the DSMB or IRB may suspend further treatment or procedures. The DSMB retain the authority to suspend additional enrollment and treatments as applicable.

A subject may also voluntarily withdraw from the study due to what he/she perceives as an intolerable adverse event, or for any other reason. If

voluntary withdrawal is requested, the subject should be asked to complete a study termination form, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or their condition becomes stable.

F. Notifying the IRB and DSMB

A Data Safety Monitoring Board (DSMB) will monitor the study for safety. The DSMB will meet periodically to review accruing safety data. The committee will consist of individuals with clinical study experience drawn from the fields of clinical immunology (specifically food allergies) and biostatistics. These individuals will be entirely independent of the conduct of the study.

The study investigator will provide the DSMB with listings of all AEs/SAEs on a periodic basis. The DSMB will meet annually to review all AEs/SAEs. Furthermore, the DSMB will be informed of all SAEs within 24 hours. Furthermore, the sponsor will inform the FDA, IRB, and DSMB of expedited reports of SAEs.

G. Reporting Criteria

The investigator will ensure the timely dissemination of all AE information, including expedited reports, to the IRB in accordance with applicable local regulations and guidelines.

9. MECHANISTIC ASSAYS

Subjects may have blood drawn and saliva collected for laboratory studies at the discretion of the investigator throughout the study. The investigator will document in the database the rationale for each sample. Examples include: checking mechanistic studies for subjects who develop specific gastrointestinal side effects (e.g. EoE), subjects who are unable to tolerate desensitization to 300 mg or subjects with severe adverse events.

The overall goals of the mechanistic studies are to identify changes in basophil, T cell, and antibody responses using peripheral blood and saliva samples from study subjects. We are especially interested in the changes in these immune compartments that are associated with treatment with oral immunotherapy for food allergy. In other words, we aim to explore the mechanisms responsible for long-term desensitization and/or tolerance to

food allergens induced by immunotherapy. Delineating its specific long-term effects on the immune reaction will enable us to determine its utility and define its therapeutic role.

We have previously demonstrated changes in peanut-specific IgE, IgG, and IgA, as well as changes in basophil activation and T cell phenotypes in subjects on immunotherapy. Peripheral blood samples from subjects will be collected in this protocol to further follow these subjects' immune responses to the food.

Blood collected in serum separator tubes will be centrifuged and serum collected and stored at -80°C until use. Serum will be used to study allergen-specific IgE, IgG, and IgA quantities, epitope specificity, and blocking function. Blood collected in heparin-containing tubes will be used to isolate peripheral blood mononuclear cells (PBMCs) using a Ficoll gradient. PBMCs will be stimulated *in vitro* with allergens and used to assess changes in T cell frequency, phenotype, and function. Heparinized blood will also be used to determine basophil activation responses by *ex vivo* stimulation and assessment via flow cytometric techniques.

Saliva will be assessed for total and allergen-specific IgA and Secretory-IgA (sIgA) quantities. Saliva samples will be frozen it at -80 C until analysis.

10. Statistical Considerations and Analysis Strategy

A. Interim and Final Analyses

An interim analysis will be performed when at least 50 patients have finished their peanut OIT treatment phase and at least 25 patients finished 6 months of food equivalent treatment phase.

The interim analysis and the final analyses will include all subjects in the study who provided complete follow up information regarding their

compliance and adverse events, and will also include those who dropped out or were withdrawn from the study before its completion.

The final analyses will be performed when all subjects have completed the study.

B. Plans for Each Specific Aim

Aim 1. Investigate the safety and compliance in the 2-stage protocol in subjects who either (a) have previously developed desensitization and then subsequently lost this protection due to a period of time off of therapy, or (b) have previously endured an extended time on placebo therapy.

We will rely on the following methods to accomplish Aim 1:

1. Our primary analysis will focus on estimates of incidence rates of adverse events and the proportion of days of treatment missed during the treatment protocol.
2. Our secondary analyses will include estimation of

    - the overall incidence rate of gastrointestinal AEs during the entire 2-stage treatment sequence.
    - the overall incidence rate of Epipen use
    - the overall incidence rate of drop-outs due to gastrointestinal AEs during the entire 2-stage treatment sequence.

3. Exploratory analyses will be used to investigate potential candidate risk factors for AEs (using logistic regression models) and causes of missed treatment days (using generalized log-linear models for counts of days).
4. Descriptive tabular and graphical methods will be used to visualize the data and examine the relationships among the measures of interest using graphical and descriptive methods.

All statistical estimates will be tabulated with the corresponding 95% confidence intervals (CI). Interpretation of these CIs will be an integral part of the analyses. For Aim 1 (and for all the aims) sensitivity analyses will be performed to evaluate the robustness of the main results to reasonable perturbations of the choices of statistical methods and statistical assumptions used. For example, the influence of any extreme or questionable data value will be explored. Results of the sensitivity analyses will only be used to guide our level of confidence in the main results.

Aim 2. Characterize and compare the two stages of the protocol in terms of safety and compliance.

We will rely on the following methods to accomplish Aim 2:

1. Our main analyses will focus on stage-specific estimates of incidence rates of adverse events and the proportion of days of treatment missed. Comparisons of the two stages will rely on logistic regression models for rates, and generalized log-linear models for counts of days. The primary emphasis will be on point estimates and confidence interval estimates. No hypothesis tests will be performed.
2. Our secondary analyses will include estimation of

- the stage-specific incidence rates of gastrointestinal AEs during the entire 2-stage treatment sequence.
- the stage-specific incidence rates of Epipen use
- the stage-specific incidence rates of drop-outs due to gastrointestinal AEs.

Comparisons of the two stages will rely on logistic regression models for rates, and generalized log-linear models for counts of Epipen usages. The primary emphasis will be on point estimates and confidence interval estimates. No hypothesis tests will be performed.

3. Exploratory analyses will be used to investigate potential candidate risk factors for AEs (using logistic regression models) and causes of missed treatment days (using generalized log-linear models for counts of days).
4. Descriptive tabular and graphical methods will be used to visualize the data and examine the relationships among the measures of interest using graphical and descriptive methods.

Statistical estimates of interest include stage-specific parameter estimates (e.g., incidence rates) as well as estimates of differences between stage-specific parameters (e.g., odds ratios, or rate differences). All statistical estimates will be tabulated with the corresponding 95% confidence intervals (CI). Interpretation of these CIs will be an integral part of analysis. For Aim 2, sensitivity analyses will be performed to evaluate the robustness of the main

results to reasonable perturbations of the choices of statistical methods and statistical assumptions used.

Aim 3. Explore the mechanisms responsible for long-term desensitization and/or tolerance to food allergens induced by immunotherapy.

We will rely on the following methods to accomplish Aim 3:

1. Our main analyses will focus on changes in basophil, T cell, and antibody responses in peripheral blood and saliva samples. The exploratory analyses will be used to generate or refine hypotheses. No hypothesis tests will be performed.
2. Descriptive tabular and graphical methods will be used to visualize the data and examine the relationships among the measures of interest using graphical and descriptive methods.

All statistical estimates will be tabulated with the corresponding 95% confidence intervals (CI). Interpretation of these CIs will be an integral part of analysis of the primary outcome.

For Aim 3, sensitivity analyses will be performed to evaluate the robustness of the main results to reasonable perturbations of the choices of statistical methods and statistical assumptions used.

C. CHOICE OF SAMPLE SIZE

The choice of sample size is based entirely on the ethical necessity of providing therapy to a pre-defined number of individuals in need of salvage therapy. We anticipate that up to 100 eligible subjects will be enrolled to receive the proposed salvage treatment regimen.

11. DATA MANAGEMENT AND DATA HANDLING:

A. RESEARCH DATA MANAGEMENT

Management of the research data for this study will involve collection, entry, processing, storage, retrieval, archival, distribution and documentation of

information collected according to a written protocol. The overall strategy for quality assurance in data management will be of a professional level as described in the following sections.

B. Plan for Ensuring Confidentiality

Study records will be kept confidential as required by law and institutional policies. All research data and records are stored in the Food Allergy database, on the UNC Pediatric Allergy / Immunology server, and/or research study binders. Participants' personal identifying information will be accessible only to the investigator and authorized study personnel. Research data will be identified only by study identification numbers (IDs). These study IDs will be used to maintain relationships in the data between various tables. All consent forms and any paper data collection instruments will be stored in a locked cabinet in a secure location. The list identifying subjects with their contact information will be kept separate from the scientific study data. The database will be created within centralized files and maintained on University approved, encrypted, password protected, shared research drives and will be viewed only on approved devices by approved study personnel. To ensure PHI Security, procedures to maintain privacy and confidentiality will be followed rigorously. For each subject, identifying information and protected health information (PHI) will be collected along with scientific study data. Each research subject will be assigned a study identification number (ID). The scientific study data will be stored in a digital file that does not include patient identifiers or PHI. A separate data file will contain identifiers and PHI. A master file linking patient identifiers to the study data will be kept under lock and key by principal investigator. The database will be password protected and will be stored on servers housed in a secure location.

C. Plan for Ensuring Data Security

The research binders, including source documents, are kept locked in the study team's office suite. The subject's information is accessible only to the investigator and authorized members of his designated research study team by password protection or direct viewing of the research record.

D. Plan for Quality Assurance

The investigators will keep accurate records to ensure that the conduct of the study is fully documented. The investigator is responsible for regularly reviewing the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data. The P.I. will have overall responsibility for ensuring quality in the data and in the procedures that produce the data. In addition to the master protocol document, written guidelines and detailed procedure manuals may be needed for uniform adherence to the detailed intent of the protocol. The written record of how the study was performed will be completed prior to commencement of recruitment and will be updated during the course of the study. The P. I. will have overall responsibility for the definition and production of the documents necessary to describe all aspects of the study in sufficient detail to insure the study can be conducted in a scientifically sound, standardized manner. The P.I. will be assisted by members of the research team in monitoring adherence to protocol.

E. Data Handling Procedures

Case Report Forms (CRFs). As it is not unusual for revisions to the CRFs to occur in clinical studies, each form will be clearly labeled with a version number. Transition to an updated version of a CRF will be communicated to all members of the research team.

Data Collection. Study data will be recorded at the point of care using data collection instruments provided by the study team. Paper forms will be stored in a designated folder securely maintained at the point of care and will be retrieved by the study team on a daily basis. The subjects' medical records will be retrospectively reviewed to obtain study data and the patient characteristics at admission. The medical record data will be recorded on a patient-specific CRF. Data collection will adhere to precise written instructions and will be monitored to insure adherence to the protocol.

Data Entry. All data entered into the database from the CRFs will be verified by comparing the original CRFs to the values in the database.

Data Editing. The P.I. will be responsible for reviewing data-monitoring results and investigating questions raised (i.e., "queries") about remarkable or questionable data values.

Database Documentation. The names of the variables and their valid ranges or categorical values will be listed in a "data book". Documentation will also include an index of computer programs and an index of reports. All programming for statistical computation will include comments providing internal documentation.

Pilot Testing of Operations. All aspects of data management and project operation will be pilot tested prior to the commencement of the study in order to verify adequacy of the methods, materials and systems prepared. Every clinical study collects such pilot data –either intentionally prior to commencement of the study, or unintentionally after recruitment has begun.

F. Risk of Deductive Disclosure

We will minimize the risk of unauthorized persons using the database to figure out a subject's identity and responses.

(1) The database will comprise two separate files: a TRACKING FILE (containing sensitive patient identifiers such as name, birthdate, date and time of admission to the ER, and Subject_ID) and a de-identified RESEARCH FILE containing non-sensitive data such as Subject_ID, age at admission to the ER, elapsed time since admission to the ER, treatment assignment, pain scores, questionnaire data, etc. Both database files contain Study_ID. This allows the two sets of information to be linked together if necessary, but prevents linkage as long as the two files are kept safely separated.

(2) The database will be secured on encrypted storage media to guard against hacking or other unauthorized access. Paper forms will be stored in locked locations.

(3) Data will be retrieved from the RESEARCH FILE and distributed to specific personnel (e.g., the P.I., or co-investigators) for purposes of statistical computations for preparation of publications. Storage, retrieval and distribution will be carefully and securely controlled. Digital

transmission of the data will be encrypted. Transportation of the data will use secure media.

(4) Selective data-entry will also be employed: Some of the study data does not need to be entered into an electronic file and will be maintained on paper forms in a locked storage location.

12. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

A. Statement of Compliance

This study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the consent documents will be reviewed and approved by the UNC IRB. Any amendments to the protocol or to the consent materials must also be approved before they are implemented.

B. Consent and Assent

The consent process is a means of providing information about the study to a prospective participant and/or to the participant's parent/guardian and allows for an informed decision about initial and continued participation in the study. A copy of the consent will be given to a prospective subject or parent/guardian for review. The study staff will review the consent and answer questions. The prospective subject or parent/guardian will be told that being in the study is voluntary and that he or she may withdraw him/herself or his/her child from the study at any time, for any reason. Subjects or parents/legal guardians (if subject <18 years old) will be asked to read, sign, and date a consent form before entering the study or undergoing any study-specific procedures.

Participants 7 years and older will be asked for assent to participate in the study. The consent form must be revised whenever the protocol is amended with a study design change.

C. Privacy and Confidentiality

Study personnel respect participant's privacy and confidentiality throughout the study. Each participant will be assigned a unique study identification number. The participant's study identification number is used for purposes of data and specimen collection and storage. The study identification number

is used for specimen labeling, including specimens sent to laboratories for assays. The participant's study identification number may be used when information is shared with collaborators for research purposes, for scientific meeting presentations, and/or for publications.

Study participants' information will only be shared using the unique study identification number; all other personal identifiers will be removed prior to the release of information. Information and data resulting from this study may be presented at scientific meetings or published and, the participant's identity will not be revealed, but the participant's unique identifier may be used.

Study participation may involve testing that is considered clinical standard of care, as well as testing that is solely for research. Specimens sent to clinical laboratories for testing may contain the participant's name. Standard of care clinical test results may be entered in the participant's medical record. The results of tests and assays conducted solely for research will not be entered in the patient's medical record.

Except for when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of UNC.