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HUMAN SUBJECTS RESEARCH PROTOCOL - RESEARCH SUMMARY (SUPP N)

DATE: 6/1/2016
TITLE OF PROJECT: Use of amplification in children with unilateral hearing loss
PRINCIPAL INVESTIGATOR: Nikhila Raol, MD and Michael Cohen, MD
FUNDING SOURCE: Research fund, Dr. Michael Cohen, pediatric otolaryngology

BACKGROUND

1) Discuss the following in paragraph format

- Discuss the importance of the topic (public health and/or clinical importance and impact on individuals/community; incidence, prevalence, mortality and morbidity)
- Critically appraise the relevant literature and discuss the state of current knowledge on the topic (including deficiencies in knowledge or gaps that make the study worth doing)
- Describe, in detail, your approach to address the research question
- Explain how your study will contribute to existing research and benefit other individuals or the wider community

RESPONSE:

Unilateral hearing loss (UHL) is defined as decreased hearing in one ear, with normal hearing thresholds in the contralateral ear. Approximately 0.83/1000 newborn children are found to have UHL. It is estimated that about 3-5% of all children in the United States are eventually diagnosed with UHL. When the cutoff for normal hearing is placed at 15 dB, this incidence is as high as 6.3%, which corresponds to a prevalence of 6.2 million children nationally. The management of UHL continues to be an area of debate, as the handicap associated with UHL is often underestimated. In fact, those with UHL often go without assistance due to lack of recognition of the disability by some health and educational professionals, who have claimed that this hearing loss "attracts little attention from either patient or parent" and that "these children experience few communicational or educational problems." However, in evaluation of children with permanent hearing loss, rates of children who need speech/language intervention and aural rehabilitation are not significantly different between those with bilateral permanent hearing loss and those with unilateral permanent hearing loss. Unfortunately, children with UHL are half as likely to be referred for hearing testing as those with bilateral hearing loss.

Studies have demonstrated the negative impact of unilateral hearing impairment in children. Educational and behavioral difficulties have been clearly shown, with a number of studies demonstrating increased rates of failure of at least one grade in children with UHL when compared to their classmates with normal hearing (24-35% vs. 3.5%). Additionally, increase in special educational needs (12-41%)

and frequent problems with behavior have also been noted in this population. In several studies, Lieu and colleagues have shown poorer performance for children with UHL. In a study looking at oral and written language scores, children with UHL did significantly worse than their siblings, who served as matched controls, on language comprehension, oral expression, and oral composite scores. In addition, these children were four times more likely to have Individualized Education Plans (IEPs) and twice as likely to have received speech-language therapy.

Despite these findings regarding the impact of UHL on children, there is a paucity of literature to support or refute the efficacy of hearing aid use in improving measurable academic, behavioral, or quality-of-life (QOL) outcomes. While hearing related disease-specific quality of life measures for children were not developed until very recently, previous studies in adults with UHL reported decreased quality of life, with increased frustration and shame due to hearing disability. The Hearing Environments and Reflection on Quality of Life questionnaire, or HEAR-QL, an instrument developed and validated at Washington University in St. Louis for young children with hearing loss initially (2011) and then later for adolescents (2013), examined effects on environments, activities, and feelings of children with both unilateral and bilateral hearing loss. Significantly lower scores, indicating poorer quality of life, were seen in patients with both UHL and bilateral hearing loss. Interestingly, differences in quality of life between children with UHL and children with bilateral hearing loss were found to be significant in only 1 out of 3 subdomains.

A 2010 study by Johnstone et al. demonstrated that children with UHL who used amplification at a young age (6-9 years) had improvement in localization acuity, while those who received amplification at an older age (10-14 years) noted impairment in localization. This may indicate that the timing of initiation of amplification in UHL may play an important role in whether the intervention is beneficial. In addition, Noh and Park's study in 2012 demonstrated that children with UHL needed to sit 3.5 meters closer to the teacher to obtain the same speech discrimination scores as children with binaural hearing. While this can be accomplished in a small room setting, this may not be possible at all times in all classes, and it is certainly not translatable to hearing environments outside of the classroom. It is not clear whether adding amplification to would eliminate this handicap and improve quality of life, behavior, or academic performance.

Current interventions:
Multiple options exist for management of UHL. Preferential seating in the classroom is often the first line of treatment utilized, placing the child at the front of the classroom with the better hearing ear toward the teacher. Evaluation of the classroom by an educational audiologist or other specialist in the education of children with hearing loss in order to optimize the listening environment is another commonly utilized modality for manging UHL. Interventions such as carpeting, tennis balls placed on the legs of chairs, and selection of a classroom with lower ambient noise levels from outside traffic or air handling equipment can reduce significantly improve signal to noise ratios for the student. Another modality for improving signal to noise ration is use of a frequency-modulated (FM) system in the

classroom, which specifically amplifies the teacher's voice via a microphone worn by the teacher. This increases the signal-to-noise ratio for the teacher's voice as it does not amplify background noise. Differentiating relevant sound signals from background noise a particularly challenging problem for children with UHL. Other options for management of UHL include various forms of amplification including a unilateral hearing aid, contralateral routing of sound (CROS) systems, and potentially cochlear implantation (though this practice has not been widely adopted in children with UHL in the United States).

In the only study to date comparing the above modalities to one another, Updike compared speech perception measures in 6 children, ages 5 to 12 years, with mild to profound UHL with use of FM systems, CROS aids, and conventional hearing aids. He concluded that FM systems were beneficial in all hearing situations and in all degrees of hearing loss. In addition, he stated that neither hearing aids nor CROS aids provided benefit in speech understanding, and both may worsen speech perception in noisy situations. Multiple limitations exist with this study, including a small sample size and lack of a time period for the patients to adjust to the use of amplification.

In studies looking at acceptance of hearing aid use in children with UHL, children with mild to moderately severe hearing loss tended to accept hearing aids, while those with severe to profound hearing loss were less accepting. Parental satisfaction with hearing aids in this population has been good, with many noticing improved hearing for their children. More recently, Briggs et al. published a study looking at 8 children, ages 7 to 12 years, with mild to moderately severe UHL, who were aided with digital hearing aids. Although speech perception scores did not show significant improvement, parents subjectively reported significant improvement in quality of life after 3 months of use. In one German study of 3 children with severe to profound unilateral hearing loss, improvement in speech understanding in noise and sound localization following cochlear implantation was observed and subjective improvement was reported by parents.

Compliance with use of amplification should also be considered in these cases, as Fitzpatrick et al. demonstrated in a study of 670 children with unilateral or bilateral hearing loss. While amplification was recommended in 90%, less than two-thirds of the children wore their hearing aids consistently.

To date, only two studies exist which examine the use of amplification in children with unilateral hearing loss. Both studies are limited by small sample size. In addition, the earlier study evaluated analog hearing aids, whereas in the present day, digital hearing aids are widely used, and was further limited by a very short study period. Our study proposes to examine whether children with UHL note improved quality of life when using amplification via a hearing aid in conjunction with conventional classroom accommodations including an FM system.

In our study we will compare the use of conventional measures to conventional measures plus a digital hearing aid on the affected ear using validated quality of life instruments administered to the subject, the

subject's teacher, and the subject's parent. The instruments used will be the HEAR-QL, the CHILD, and the LIFE-R.

The HEAR-QL consists of 28 items that measure the perceived effect of hearing loss on the quality of life. It is adjusted to a scale of 0-100, with lower scores indicating a worse disease-specific quality of life and higher scores signifying a better disease-specific quality of life.

The CHILD questionnaire consists of 15 questions that describe situations where hearing difficulty may occur when the child is with his/her family. The answers are measured on a scale of 1-8, with 1 indicating poor ability to hear, and 8 indicating complete understanding. The scores are added and divided by 15, giving a final score on a scale of 1-8. Two versions, the CHILD (child) and the CHILD (parent) are phrased to apply to the child and the parent respectively.

The LIFE-R questionnaire consists of 15 questions that describe situations where hearing difficulty may occur in school. The answers are measured on a scale of 0-5, with 1 indicating situations in which hearing is always difficult and 5 indicating situations where hearing is always easy. The scores are then added and measured overall on a scale of 0-75. Two versions, the LIFE-R student and the LIFE-R teacher are phrased to apply to the student and the teacher respectively.

Each of the surveys will be administered five times in total: at the time of enrollment, once at the midpoint of the first treatment arm, once after completion of the first treatment arm, once at the midpoint of the second treatment arm, and once after completion of the second treatment arm. Comparisons will then be made among groups as described later in this proposal.

Our practice is well suited to carrying out this study as we are a tertiary care center serving a large region. Our multidisciplinary pediatric hearing loss clinic allows children to be evaluated and longitudinally followed in conjunction with the audiology, speech and language pathology, neuropsychology, and medical genetics. In the past year, there were over 300 visits coded for unilateral hearing loss based on ICD-9 codes, with 70 unique patients, making recruitment of our target sample size over the 3-year study period feasible. The potential impact of this study is great, as there is no consensus as to whether amplification should be recommended for children with unilateral hearing loss, and a study of this power would serve as a useful guide in this decision-making process.

AIMS

2) Your aim(s) should arise from your literature review and state what the study hopes to accomplish.

RESPONSE: Our study aims to evaluate the impact of hearing aid use on subject-reported quality of life, teacher perception of listening ability, and parent perception of hearing ability in children 6-12 years-of-age with UHL. We hope to determine whether the addition of a hearing aid strengthens or worsens performance in the above domains in the study population in comparison to standard measures including FM system and preferential seating in the classroom.

OBJECTIVES

3) Your focused research question needs to be further refined into one or more study objectives. The study objective(s) should be single and quantifiable statement(s) that will allow you to answer your research question.

RESPONSE: Objective 1: To evaluate the impact of hearing aid use in children 6-12 years-of-age with UHL with respect to subject-reported quality of life. Objective 2: To evaluate the impact of hearing aid use in children 6-12 years of age with UHL with respect to classroom performance. Objective 3: To evaluate the impact of hearing aid use in children 6-12 years of age with UHL with respect to parental perception.

HYPOTHESES

4a). Primary Hypothesis - Hypotheses are more specific than objectives and amenable to statistical evaluation. Your primary hypothesis is your statement of the hypothesized effect on the primary outcome measure. A hypothesis is worded very simply and written as 'testable' statements. Your experimental results will prove or disprove your hypothesis. Hypotheses are generally stated in the null form (H_o) as they have their basis in inferential statistics. Rejecting the null hypothesis increases our confidence, with a given level of probability, that there is a relationship between the variables being studied. However, a classic scientific hypothesis includes both a null and alternative (H_a) hypothesis.

**e.g. H_o: Asthma prevalence rates are not different among children from low and high socioeconomic groups in Istanbul. H_a: Asthma prevalence rates are different among children from low and high socioeconomic groups in Istanbul.*

RESPONSE: Ho: Hearing aid use in children ages 6-12 years with mild to moderately severe unilateral hearing loss does not significantly affect subject reported quality-of-life based on the HEAR-QL survey instrument. Ha: Hearing aid use in children ages 6-12 years with mild to moderately severe unilateral hearing loss does significantly affect quality of life based on the HEAR-QL survey instrument.

4b). Secondary Hypotheses - Although a study is usually based around a primary hypothesis, secondary hypotheses may also be pre-specified although based on outcomes of lesser importance or additional interest. As the primary hypothesis is usually the basis for statistical power calculations, secondary hypotheses with insufficient power will generally not lead to statistically robust conclusions.

RESPONSE: Ho: Hearing aid use in children ages 6-12 years with mild to moderately severe unilateral hearing loss does not significantly affect classroom performance or parental perception of hearing ability based on the LIFE-R and CHILD surveys, respectively. Ha: Hearing aid use in children ages 6-12 years with mild to moderately severe unilateral hearing loss does significantly affect classroom performance or parental perception of hearing ability based on the LIFE-R and CHILD surveys, respectively.

STUDY DESIGN

5) State the design of the research (e.g. randomized controlled study, cross-sectional survey, prospective or retrospective cohort/case-control).

**Whatever the study design, you need to ensure that you provide the reader with a clear statement and description of your proposed design. You may also explain why the particular study design has been chosen in preference to other possible designs (i.e. justification for choice of study design)*

RESPONSE: Randomized Cross-Over Clinical Trial.

ELIGIBILITY CRITERIA

6a). Inclusion Criteria - Inclusion criteria are the 'characteristics' that clearly describe the study population that are required for a subject to be included in the study. The criteria may be based on factors such as age, gender, the type and stage of a disease, previous treatment history, and co-morbid medical conditions. They may state appropriate criteria for admitting special 'at-risk' populations such as women of reproductive age, children or patients with disease states or organ impairment.

RESPONSE: Children ages 6-12 years with mild to moderately severe unilateral hearing loss, with thresholds across 4 frequencies ≥ 25 dB but < 70 dB in the worse hearing ear; Normal hearing in the contralateral ear, defined as thresholds ≤ 20 dB from 250 Hz to 8000 Hz; Unaided word recognition scores of ≥ 80% in worse hearing ear

6b. Exclusion Criteria - Provide details of participants that will be considered ineligible to participate and justification for their exclusion. These criteria are not always clinical in nature, aiming principally to accommodate participants in a safe and ethical manner. Criteria may include circumstances that interfere with the participant's ability to give informed consent (diminished understanding or comprehension, or a language other than English spoken and an interpreter unavailable), contraindications to the study treatment(s)/procedure(s), taking certain concomitant medication(s), or conditions that interfere with a patient's ability to comply with all treatment(s)/procedure(s).

RESPONSE: Contralateral hearing loss; significant cognitive impairment; Middle ear disease that has not been addressed; Inability to commit to treatment program

STUDY OUTCOMES

7a). Primary Outcome - The primary outcome should be the most important and clinically relevant outcome (e.g. clinical, psychological, economic, or other) of the study. This is the measure used to answer your study aim. However, it is also the outcome used to calculate study sample size and power and test the primary research hypothesis. Generally, no more than 1-2 primary outcome measures are pre-specified. Primary outcome measures may be measured in various ways such as: binary (e.g. caesarean/no caesarean, blood loss ≥500mL/blood loss <500mL); continuous (e.g. weight - kg, blood loss - mL); ordinal (e.g. pain - mild, moderate, severe); time to event (e.g. survival), and counts (e.g. number of infections, number of events occurring).

RESPONSE: The primary outcome measure is the score on the HEAR-QL for each group

7b). Secondary Outcome(s) - Secondary outcome(s) are measures of additional or less important research interest. They may include additional clinical, psychological, economic, or safety outcomes (e.g. treatment related side effects/adverse events). However, as these endpoints are not used to calculate study power and sample size it is often not possible to draw robust conclusions from the results.

RESPONSE: Secondary outcome measures include subject-, teacher-, and parent-reported scores on the CHILD and LIFE-R questionnaires.

STUDY PROCEDURES

8) In this section you need to clearly and comprehensively describe exactly what will happen to participants once they are enrolled in your study. Depending on the study it might include how potential participants will be approached, when they will be randomized, the frequency and duration of visits or whether they are expected to self-complete a daily diary at home, the duration of the study or follow-up, and any measurements taken at each visit (e.g. questionnaires, physical measurements, biological samples).

You should include precise details of the treatment(s)/intervention(s) intended for each group/participant. You should also provide details of any follow-up schedule (i.e. time between visits) and consider how you will monitor participants' adherence with the treatment schedule. You might also describe under which circumstances participants may be withdrawn and how this will occur. A schematic diagram or flow chart may be useful for this section.

RESPONSE:

Recruitment

Study participation will be offered to patients presenting to the pediatric otolaryngology clinic at the Massachusetts Eye and Ear Infirmary and Boston Children's Hospital based on the above criteria over a 3 year period. Patients will also be recruited by searching existing records for patients meeting the study criteria seen during the last 3 years and contacting these patients to offer study participation. Informed consent will be obtained from a parent for the child's participation in this study. Assent will be obtained from all subjects.

Interventions

At the time of entry into the trial, demographic data including age, sex, and ethnicity; past medical history; otologic exam findings; and audiogram results will be collected. The audiogram will be performed by a senior audiologist at Mass Eye and Ear, Heidi Leonard. The subject will be fitted for a hearing aid by Dr. Leonard prior to entrance into arm 2 (see below) of the study.
Subjects will participate in each of two arms of this study, with each child serving as his/her own control. Each arm will last 3-months; the order of participation will be randomized on the day of enrollment.

Conventional measures arm (arm 1): In the first arm of the study, the child will utilize conventional measures for management of unilateral hearing loss, including an FM system and preferential seating in the classroom. While two basic types of FM systems exist, personal and sound field, subjects in our study will utilize a personal FM system, worn at the ear-level. This will increase the likelihood that the child will receive amplification in all classes, and will help to standardize this intervention. The HEAR-QL, CHILD (child) questionnaire, and LIFE-R student questionnaire will be administered to the child at the beginning, midpoint, and conclusion of this 3-month arm. The CHILD (parent) questionnaire will be administered to the parent and the LIFE-R teacher questionnaire will be administered to the teacher at the same intervals. All questionnaires will be administered via REDCap to ensure that responses remain confidential.

Conventional measures + hearing aid arm (arm 2): In the second arm, the child will use the conventional measures described above in addition to a digital behind-the-ear hearing aid with a standard ear hook and custom ear mold on the affected ear. The hearing instrument will be customized appropriately for the subjects specific hearing loss by an MEEI or BCH audiologist. The subject will be instructed wear the hearing aid both at home and at school. In both arms, the FM system will be used in school only. As in the first arm, the HEAR-QL, CHILD (child) questionnaire, and LIFE-R student questionnaire will be administered to the child at the beginning, midpoint, and conclusion of this 3-month arm. The CHILD (parent) questionnaire will be administered to the parent and the LIFE-R teacher questionnaire will be administered to the teacher at the same intervals. All questionnaires will be administered via REDCap to ensure that responses remain confidential.

Exploratory BKB-SIN Assessment: Participants in both arms will be offered to participate in an optional BKB-SIN evaluation, a speech in noise test for children. This specialized audio recording will be administered to the study participant once by one of our study audiologists at either one of their scheduled visits, or during a separate study visit. The de-identified results will be recorded and securely stored with the study audiologists. The exploratory BKB-SIN Assessment will serve to inform clinicians on administering the BKB-SIN on pediatric patients with unilateral hearing loss. Participants who participate in the exploratory BKB-SIN assessment will receive a compensation of $50.

F/u will be scheduled at the completion of each 3-month period in order to perform assessment of intervention. In addition, contact by phone or email will be made at the 6-week mark in each arm (when a survey is to be filled out) in order to ensure compliance and address any problems that may be occurring. If the patient has not been compliant at the 2-month mark, they will be removed from the study. In the event of removal from the study, the patient will be asked to return the hearing aid and can then return to normal activity.

9) Randomization (if applicable)
Include the method (including any software) used to generate the random allocation sequence. Describe type of randomization performed, ratio of assignment to groups, block size permutation and stratification if applicable. Explain the methods used to conceal group allocation until assignment. Also, include information on who will generate the allocation sequence and who will assign participants into their groups.

This section should also discuss if participants, the investigator, and those assessing/analyzing the outcome(s) will be blind (or masked) to group assignment or if the study will be an open-label study (investigators and subjects know their assigned group).

RESPONSE: Subjects will be randomized for the order of participation in the two study arms using the Apple iOS random number generator. An odd number will result in the subject starting with arm 1 and an even number will result in the subject starting in arm 2. The study will be open-label as it is not practical to blind subjects, teachers, and parents as to whether a hearing aid is being used.

10) Study Specific Procedures: List all procedures (interventions, tests, surveys, etc.) to be performed ONLY for research purposes

RESPONSE: Hearing aid use, HEAR-QL assessment, CHILD assessment, LIFE-R assessment, BKB-SIN assessment

11) Standard of Care Procedures: Clearly list all standard of care (standard therapy) procedures (interventions, tests, etc.) to be performed regardless of the subject's enrollment in the study, but that will be included in the research assessment.

RESPONSE: Use of an FM system and classroom accommodations, including preferential seating

MEASUREMENT TOOLS

12) It is essential to state how the data will be collected to assess the primary and secondary outcome(s) of the study (e.g. patient questionnaire, medical charts, routinely collected hospital/research database, biological specimens). Describe at what point(s) of the study data collection will occur. You should make statements that justify the validity of the study measure/instrument. If not, you will have to verify how you will ensure the validity and quality of data being collected. Also, mention here if you are going to have one or more assessors to collect data, their level of training/experience (or how they will be trained), and if you are planning to assess inter-rater reliability (if applicable).

RESPONSE: Primary outcomes will be assessed via the HEAR-QL questionnaire, a validated and reliable instrument for children with hearing loss. Secondary outcomes will be assessed via the CHILD (child) and LIFE-R student questionnaires, CHILD (parent) questionnaire, the LIFE-R teacher questionnaire. The surveys will be administered five times in total: at the time of enrollment, at the midpoint of the first arm, after completion of the first arm, at the midpoint of the second arm, and after completion of the second arm.

13) Sample size and statistical power - A sample size or power calculation should be performed. This calculation is used to estimate the number of subjects required to answer your primary study hypothesis with an accepted power. Conversely, it also allows you to estimate what power can be achieved with a limited number of participants. This number is calculated by specifying the magnitude of the effects that are expected (i.e. informed and clinically significant), variability of the measurements and the acceptable degree of type I and II errors. You need to specify the assumptions made for the calculation. It is recommended that you consult with a statistician for this section. Also keep in mind the estimated recruitment rate and whether you need to adjust for anticipated non-responders and losses to follow up.

RESPONSE: The planned sample size (n=104) is based on achieving 80% power to demonstrate a 10-point difference in the HEAR-QL score. However, given that the child will serve as their own matched control, a sample size of 52 will give adequate power for the study. Assuming 20% of patients lost to f/u or noncompliance, at least 65 patients will need to be recruited for the study to adequately power the study. However, in order to increase power, we will attempt to enroll a total of 100 patients.

14) Statistical methods - The statistical methods used for the study objectives/hypotheses (e.g. t-test, chi-squared, multivariate modeling) must be sufficiently detailed. If conducting a randomized controlled study, you should state whether methods will include an "intention to treat" (ITT) analysis, per protocol analysis, or both. An ITT analysis is preferred as it compares all subjects in the groups to which they were originally randomly assigned (despite withdrawal, treatment failure or cross-over). Consultation with a statistician is strongly recommended. See Harvard Catalyst Statistical Consulting for more information.

RESPONSE: A two-tailed student's t-test will be used to measure the significance of the difference in survey scores between the two arms. Specific comparisons will include: arm 1 midpoint to arm 2 midpoint, arm 1 endpoint to arm 2 endpoint, and each arm test point to baseline. Analysis will be based on ITT, whether or not the study interventions are complied with.

DATA SAFETY MONITORING PLAN (DSMP)

Complete question 15 **OR** 16 depending on the risk of the study. If your study is submitted as minimal risk and determined by the HSC to be more than minimal risk you will be asked to complete question 16 during the review process.

15) If the research is **no more than minimal risk**, please describe any provisions in place to ensure the safety of participants and the validity and integrity of data. If safety monitoring will occur a safety monitoring plan may include elements such as: parameters for safety review, the frequency in which safety review will occur, the person(s) responsible for safety review, and the plan (including the person(s) responsible) for reporting adverse events, protocol deviations, or noncompliance to the HSC and others (where applicable). Data monitoring may include the specific elements that will be reviewed (e.g., informed consent documentation, verification of the accuracy of data), the frequency of data monitoring, and the person(s) responsible.

RESPONSE: From a PHI standpoint, all data will be stored on password-protected drives on MEEI secure storage. Only Drs. Cohen and Raol will have access to all the data, and PHI will be stored on a separately sheet with a patient identifier key used to correlate survey data and PHI. Use of a hearing aid is a non-invasive intervention. Risks associated with hearing aid use are minimal and include itching or irritation at the hearing aid site.

16) If the research is **more than minimal risk**, a more detailed data and safety monitoring plan is required. Please detail the plan for this study below:

QUESTION	RESPONSE

Please identify the types of monitoring (e.g., centralized[1] , on-site[2], a mix of both) that will be utilized for this study and the rationale for use (why these practices are appropriate given the nature (e.g., multisite) and risk of the study): *If a multisite study* and centralized monitoring practices will be employed, describe how processes and expectations for site record keeping, data entry, and reporting will be communicated (e.g., through a Manual of Operations and/or SOP's):	Click here to enter text.
Which individual(s) or group will be responsible for data and safety monitoring (e.g., PI, specific members of the study team, independent monitor(s), DSMB)? Please be specific and indicate who is responsible for what aspects of the study, including what responsibilities are shared:	Click here to enter text.
Provide information related to the expertise and qualifications of the individual(s) and/or groups listed above relative to monitoring. Provide a description of any specific training/qualifications required for personnel carrying out monitoring activities including personnel conducting internal data monitoring, statistical monitoring, or other monitoring activities and the presence of scientific and/or clinical knowledge needed to adequately monitor the trial:	Click here to enter text.
For those who have monitoring responsibilities please describe the plan to provide mentoring, feedback, and additional training to investigators and study staff:	Click here to enter text.
If this is a multisite study, explain the plans in place to facilitate timely communication of routine monitoring results and immediate reporting of significant monitoring issues to other sites and stakeholders (i.e., CRO, IRB(s)) as well as communication from sites to monitors:	Click here to enter text.
Please explain how monitoring activities for this study will be documented (i.e., a monitoring log kept in the regulatory binder):	Click here to enter text.
How are monitoring results communicated to stakeholders (investigator(s), IRB): *Please note that the MEE HSC requires that monitoring reports be received within 5 business days of receipt by the MEE PI/study team.*	Click here to enter text.

[1] Centralized monitoring means a remote evaluation carried out by study personnel or representatives at a location other than the site(s) at which the clinical investigation is being conducted.

[2] On-site monitoring means an in-person evaluation carried out by study personnel or representative(s) at the site at which the clinical investigation is being conducted.

What processes are in place for addressing unresolved or significant issues (e.g., significant noncompliance with the protocol) identified by monitoring at MEE or across study sites (when applicable):	Click here to enter text.
If applicable, describe the composition of the Data and Safety Monitoring Board (DSMB) including each member's relevant expertise, experience in clinical research and in serving on other DSMB's and the absence of serious conflicts of interest. Explain if any of the members have relationships with those sponsoring, organizing, conducting or regulating the trial and the nature of these relationships or if the members have no involvement in the design and conduct of the study: Note whether or not a DSMB is required (e.g., by the funding agency): Note whether or not a DSMB Charter exists for this study and include it as an appendices or indicate if it will be submitted separately to the HSC at a later date (if for example, the charter will be developed by the DSMB at the initial meeting):	Click here to enter text.
Address the process for communication of Data and Safety Monitoring Board determinations to the investigator and to the HSC:	Click here to enter text.
If applicable, please describe the electronic data capture systems you will be using and what training will be provided for those who will be using these systems:	Click here to enter text.
Include specific data elements (e.g., review of informed consent documentation, confirmation of subject eligibility) that will be reviewed:	Click here to enter text.
Specify the frequency of data monitoring (a specific number of times, at defined time points, after a certain number of subjects have been recruited or as needed):	Click here to enter text.
Who will be responsible for data review (e.g., PI, study staff, DSMB)? If this is a shared responsibility indicate which specific elements each person or group is responsible for:	Click here to enter text.
Specify the parameters (i.e., procedures, laboratory tests, or other measures) that will be used to evaluate the safety of the study treatment(s) or interventions; to include the methods and timing for assessing, recording, and analyzing these parameters:	Click here to enter text.

Specify the frequency of safety observation (a number of times, at defined time points, after a certain number of subjects have been recruited or as needed):	Click here to enter text.
Explain who will be responsible for safety review (e.g., PI, DSMB, monitor):	Click here to enter text.
Address any "stopping rules" for individual research subjects including who will be responsible for making these determinations:	Click here to enter text.
Address any "stopping rules" for parts of the study, or for the entire study including who will be responsible for making these determinations:	Click here to enter text.
Address the frequency and process for eliciting adverse event information from research subjects:	Click here to enter text.
Please acknowledge that adverse events and unanticipated problems will be reported to the HSC in accordance with the HSC policy on Reporting Adverse Events and Unanticipated Problems:	Click here to enter text.