



A Parallel, Randomized, Single-Blind, Multicenter Research Trial Comparing Early Adenotonsillectomy (EAT) to Watchful Waiting with Supportive Care (WWSC) in Children ages 5.0-9.99 with Obstructive Sleep Apnea Syndrome (OSAS)

## **MASTER MANUAL OF PROCEDURES (MOP)**

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## Introduction

Pediatric Obstructive Sleep Apnea Syndrome (OSAS) is a common health problem, affecting 2-3% of children, with rates two to four-fold higher in vulnerable populations such as African Americans. Children with OSAS usually snore loudly and have total or partial upper airway obstructions that repeatedly interrupt sleep (JAMA, June 27, 2007, Vol 297, No. 24). Untreated, pediatric OSAS is associated with a wide range of adverse health outcomes, which may lead to chronic health sequelae. Adenotonsillectomy (AT) is generally considered the first line treatment for childhood OSAS. This is the second most commonly performed pediatric surgical procedure, with OSAS the most frequent indication in academic medical centers. Nonetheless, there has not been a single randomized controlled study that has addressed the efficacy of AT. Although uncontrolled, short-term follow-up studies indicate that AT is often effective, other data indicate that residual OSAS may occur in certain subgroups, such as minority children, and in children with other OSAS risk factors, such as obesity.

A rigorous controlled study with a sufficient representation of ethnic minorities and comprehensive follow-up is needed to address the role of this treatment in pediatric OSAS, and the potential differential effectiveness among obese children and ethnic minorities. We therefore have assembled a group of expert centers in pediatric OSAS to address the hypothesis that surgical treatment (AT) of OSAS in children aged 5 to 9 years will result in measurable improvements in health outcomes measured 6 months following AT. Children eligible for AT in standard practice will be randomized to expedited (early) adenotonsillectomy (EAT) versus Watchful Waiting with Supportive Care (WWSC) with surgical treatment decisions deferred until after a seven (7) month observation period.

Funding provided by the NHLBI has resulted in the establishment of the CHAT protocol which is comprised of multiple clinical centers and specialty core groups.

<b>Name and Location</b>	<b>Site ID</b>	<b>Name ID #</b>
1. Children's Hospital of Philadelphia, Philadelphia, PA	CHOP	10
2. Cincinnati Children's Hospital, Cincinnati, OH	CINN	20
3. Rainbow Babies and Children's Hospital, Cleveland, OH	CLD	30
4. Kosair Children's Hospital, Louisville, KY	LVL	40
5. Cardinal Glennon Children's Hospital, St. Louis, MI	SLU	50
6. Montefiore Children's Hospital, A. Einstein MC, NY, NY	MNYC	60
7. Boston Children's Hospital, Boston, MA	BOST	70

### Specialty Cores

1. Data Coordinating Center, University of Pennsylvania	DCC	n/a
2. Laboratory for Clinical Biochemistry Research, Univ of Vermont	LCBR	n/a
3. Quality Control Center (QCC), University of Michigan		
Neuropsychological Quality Assurance	NPQA	n/a
Surgical Quality Control Core	SQCC	n/a
4. Scientific Coordinating Center, Case Western	SCC	n/a
PSG Reading Center	PRC	n/a

This Master Manual of Procedures (MOP) documents the elements of the randomized clinical trial to be conducted by the CHAT Project Team which aims to provide data that for the first time will address the role of AT and define the subgroups most suitable for this procedure. This study will be the first rigorously controlled and sufficiently powered study that will: a) systematically address clinically important outcomes in childhood OSAS; b) utilize a randomized controlled design; c) address a wide spectrum of OSAS; d) utilize objective and highly standardized exposure and outcome measurements; e) include a racially diverse sample, with representation of overweight and non-overweight children.

***A note about preparing staff to carry out CHAT-related procedures and data entry:***

Prior to study initiation and on an ongoing basis (as needed or annually), all clinical site personnel involved with CHAT data collection must be trained and certified in the procedural elements pertaining to their role (polysomnography techs will be trained in CHAT-specific PSG equipment, data collection and data transfer, for example). Details are listed in the Appendices of this manual under the corresponding specialty.

***Individual Training on the Data Management System (DMS)***

The designated unblinded research coordinator at each site will be trained on the DMS through 1:1 telephone instruction with a representative from the Data Coordinating Center immediately prior to study initiation and periodically throughout the trial, if needed. It will be h/her responsibility to instruct data entry personnel on the use of the DMS and to delegate data entry tasks that will not compromise the integrity of the study blind. All personnel utilizing the DMS must receive an authorization ID from the DCC.

***Staff Identification Numbers (IDs)***

CHAT-trained personnel will be assigned a unique identifier including Surgeons, Principal Investigators and CRC/CTRC staff. This will be a 4 digit number that will contain the site ID followed by a 2-digit number. The DMS will assign a block of staff IDs for each site and core (if applicable) and distribute a list. The ID should be used by all chat trained personnel who perform exams, collect, transmit and/or enter data.

***Randomization:***

Only the unblinded site coordinator will have access to the secure, password-protected randomization portal and visit schedule.

This manual is formatted to present a step-by-step chronological overview of the regulatory and procedural elements necessary to carrying out the trial from preliminary screening through the 7-8 month study period. Specialty Manuals provide detailed information about procedures related to a specific role/aspect of the study and are listed on the last page as for a reference. These are bundled separately for ease of viewing, distributing and printing and are designed to act as stand alone documents. These manuals may be copied and placed in the corresponding clinic/unit as a reference guide for CHAT-trained and certified staff.

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## **General Study Information**

### **Design, Objectives and Endpoints**

#### **Study Design and Objectives**

The CHAT clinical trial will utilize a two-arm, single-blind, randomized design to evaluate the safety of Adenotonsillectomy (AT) in the treatment of Obstructive Sleep Apnea (OSAS) as compared to Watchful Waiting with Supportive Care (WWSC).

All participants who meet eligibility criteria including:

- evaluation by an otolaryngologists (pre baseline visit )
- polysomnography (pre baseline visit)
- neuropsychological testing and clinical assessments (Baseline Visit)

Will be randomized to:

1. EAT arm : receive adenotonsillectomy (AT) within 4 weeks of the baseline visit
2. WWSC arm: defer AT until after the 7 month observational period and re-evaluation by an otolaryngologist at Month 8.

#### **Primary Objective**

- To assess the effect of early AT (EAT) surgery versus Watchful Waiting with Supportive Care (WWSC) in children with OSAS with respect to neurocognitive functioning, specifically executive/attention functions.

#### **Secondary Objectives**

- To assess the extent to which AT improves breathing disturbances and sleep quality in children with OSAS.
- To assess whether the effects of AT differ according to race and/or weight category
- To assess the effect of AT in children with OSAS with respect to behavior, physical growth, blood pressure (BP), metabolic profile, and overall quality of life.
- To evaluate the relationship of changes in breathing disturbances and sleep quality to changes in neurocognitive functioning.
- To assess the relationship of changes in breathing disturbances and sleep quality to behavior, physical growth, blood pressure, metabolic profile and overall quality of life.

#### **Overview of Timeline and Endpoints**

Approximately 460 eligible children, 230 per treatment arm will be recruited, assuming a recruitment rate of 2-4 subjects per month across clinical sites:

Strata will be created and monitored such that equal numbers of children who are overweight and of diverse race/ethnicity are recruited from each site and randomized across the groups (EAT and WWSC), with 60% minority recruitment from Cleveland and Philadelphia and 40% from Cincinnati and Louisville.

To assure that sufficient numbers of ethnic minorities (50% non white) and overweight children (50% > 95% BMI percentile) are recruited and randomized in equal proportions, children will be randomized by block design, and overweight-race specific strata will be closed once recruitment goals for those demographic groups are met.

Participants will be randomized to EAT or WWSC at baseline or within 48hours. Surgery will be scheduled for subjects in the EAT arm to occur within 4 weeks of randomization.



## **Study Phases**

### **Screening Phase**

The screening phase includes, preliminary review of eligibility (age, chief complaint and any other information available through medical chart review if applicable) ENT evaluation/tonsillar size assessment, and a PSG.

### **Enrollment Phase**

This phase occurs from the time of randomization through 7-8 month visits (end of study). All study personnel are blinded to the treatment arm assignment except the unblinded research coordinator and ENT surgeon. All participants will be closely monitored for OSAS status (e.g. worsening of symptoms) through clinical assessments including phone and clinic interviews/exams. The 7 month visit will provide data for the primary and secondary endpoints.

## **General Protocol Policy**

### **Changing the Protocol**

The objectives of the CHAT project are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure participant safety or will significantly enhance the scientific validity of the study.

### **Initiating a Protocol Change**

Any member of the CHAT project may request a change to any portion of the study protocol. The member wishing to change the protocol should present the proposed change(s) in writing to either the Chair of the Steering Committee or the Principal Investigator of the Data Coordinating Center (DCC), who will then contact the others. The DCC Principal Investigator and the Chair of the Steering Committee will then jointly decide on the appropriate mechanism (letter, conference call, or meeting) to handle the proposal depending on the implications of the proposed change. Proposed changes with only a minor impact on the current course of the CHAT project can be properly handled through a letter to each member of the Steering Committee. Proposed changes with a great impact on the course of the CHAT project will be presented to the Steering Committee via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after the Steering Committee reaches a majority vote and the NHBLI Project Officer approves of the proposed changes. Once a proposed change has been approved, the DCC will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol. Clinical Centers will then submit the protocol amendment and revised protocol to their local IRB for approval.

Substantive changes to the protocol and ancillary proposals must be submitted to the DSMB for review and approval before implementation can occur.

## **Study Organization**

### **Clinical Centers**

There are multiple clinical sites (listed at the beginning of this document)

- Cincinnati Children's Hospital, Cincinnati, OH
- Children's Hospital of Philadelphia, Philadelphia, PA
- Kosair Children's Hospital, Louisville, KY (no longer enrolling as of 10/04/08)

- Rainbow Babies and Children’s Hospital, Cleveland, OH
- Cardinal Glennon Children’s Hospital, St. Louis, MI
- Montefiore Children’s Hospital, A. Einstein MC, New York, NY
- Boston Children’s Hospital, Boston, MA

Each site is comprised of the following CHAT-trained personnel:

**Blinded to treatment assignment:**

- Principal Investigator (Clinical – Pulmonary/Sleep)
- Co-Principal Investigator - Pediatric Neuropsychologist
- Psychometrician
- PSG Technicians
- Research Assistant/Coordinator (CRC nurses/staff, assistants, if applicable)

**Unblinded to treatment assignment:**

- Principal or Co- Investigator – Pediatric Otolaryngologist
- Research Coordinator (clinical site CHAT project manager)
- Data Entry Personnel who have no contact with participant/parent/legal guardian and/or those who are not obtaining/collecting study-related data.

Additional staff involved with CHAT: It is the responsibility of the clinical site’s CHAT project manager (essentially the unblinded research coordinator) to assure that additional site personnel assisting in data collection such as clinical research unit staff/nurses are trained and certified if applicable.

One research coordinator at each site will be designated as the unblinded CHAT coordinator and, in addition to the ENT surgeon, will be the only person who knows the treatment arm assignment.

To maintain the study blind during through the month 7-8 month study period every effort must be made to keep CHAT study personnel involved with primary data collection/testing blinded to the treatment group (psychometricians, PSG/PRC staff and site PIs - including the core centers’ staff.

Sites must instruct participants and their family members not to discuss their assignment (early AT versus Waiting) and/or aspects of AT surgery with the psychometricians performing the tests, the PSG technicians, and the PIs during their clinical visits.

Families will be instructed to contact the unblinded research coordinator for questions and concerns related to study procedures during the 7 month trial.

The structure/function of site personnel may vary from site-to-site and blinding issues must be considered in order to protect the integrity of the study.

**Data Coordinating Center and Quality Control Cores**

This project involves four Quality Control/Specialty Cores who are responsible for overseeing the procedural aspects of the protocol and overall data collection and quality control.

## Data Coordinating Center (DCC)

The DCC, located at the University of Pennsylvania, will provide administrative, biostatistical, and data management/computing leadership for design/conduct of the clinical trial.

## Quality Control Cores

All Quality Control Core Centers/Staff will be blinded to the treatment arm assignment, *except Surgery*

- The **Scientific Coordinating Center (SCC)** located at the Case Western Reserve University, Cleveland, OH, will provide scientific oversight of protocol development and assist with statistical analyses and also oversee the Polysomnography Reading Center (PRC).
- **Polysomnography Reading Center (PRC)** also located at Case Western Reserve University, Cleveland OH, will provide central scoring of Polysomnography (PSG), 24 hour Ambulatory Blood Pressure (AMBP), confirm PSG eligibility and provide standardized PSG training and monitoring.
- The **Quality Control Core (QCC)** located at the University of Michigan, Ann Arbor, MI, is comprised of two entities which will provide standardized data collection, testing methods and quality control for:
  - **Neuropsychology Quality Assurance (NPQA)** for data collected from neurocognitive and behavioral testing.
  - **Surgery Quality Control Core (SQCC)** for all data collected from AT surgery and tonsillar photographs.

The QCC (NPQA and SQCC) will also oversee training and certification of psychometricians and ENT surgeons, when applicable.

- **Laboratory for Clinical Biochemistry Research (LCBR)** located at the University of Vermont, Burlington, VT, will serve as the central repository, providing storage of blood samples, laboratory analysis and quality control of specimen collection, processing and storage.

## Boards and Committees

### Data Safety Monitoring Board (DSMB)

The DSMB has been established according to NHLBI policies. Members include experts in sleep medicine, otolaryngology, biostatistics, pediatrics, neurocognition and ethics. They were selected from institutions independent of any participating site or quality core. The DSMB will convene in person on an annual basis and semi annually via conference call. Final protocol review and approval is given by the DSMB and NHLBI, and through coordination by the DCC before study initiation can begin. The DSMB will be consulted as needed to address issues related to participant safety any deviations from the protocol.

### Overview

Project committees and subcommittees will meet on a regular basis determined by the chair(s) and may vary based upon need. Meetings will be held via conference call and in some cases, in

person on an annual basis. Each committee is comprised of a chair(s) and principal investigators/co-principal investigators who are specialists in their field and members of the CHAT team. Other members of the committees are coordinators and technicians directly involved with performing study related procedures and data collection or administrative personnel from the NHLBI and DCC.

### **Executive Committee**

In multi-center studies with multiple coordinating center (e.g. clinical, data, statistical and specialty cores), there is often an Executive Committee that is responsible for reviewing study progress and identifying and resolving issues. The NHLBI Scientific (Medical) Officer and/or Program Officer are members of this committee which acts as a small study leadership group that guides the study implementation and operation.

The executive committee for CHAT is comprised of the Principal and Co-Investigators who head the project (Susan Redline, MD and Susan Ellenberg, PhD) members of the National Heart Lung and Blood Institute (NHLBI) who sponsor the project and members of the Data Coordinating Center.

### **Steering Committee**

The Steering Committee is comprised of chair (s) and PIs from each clinical center and specialty core as well as members of the NHLBI. Meetings are held at least monthly via conference call with in-person meetings held occasionally. The purpose of the Steering Committee is to address protocol-related issues and to review standard reports generated by the DCC including adverse and serious adverse events and recruitment and enrollment progress. The steering committee also receives updates from subcommittee chairs, when applicable, and monitors the overall status and conduction of this multi-site clinical trial.

The following areas typically fall under the purview of the Steering Committee:

- general design and conduct of the study
- protocol
- review of the essential study documents, including MOP and forms
- review of data collection practices and procedures
- changes in study procedures
- appointments to and disbanding of committees and subcommittees
- allocation of resources based on priorities
- review of study progress
- review and implementation of recommendations from the DSMB
- review and response to other general advice and/or recommendations (e.g., from the NHLBI Program Director)

### **Subcommittees**

The subcommittees consist of specialist in their field who coordinate activities related to the development, training and implementation of their protocol-specific areas. Over the course of the project, new committees may be formed and existing groups may be modified or dissolved based on need.

The CHAT project is sponsored by a grant from the National Center on Sleep Disorders Research (NCSDR), National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, Maryland.

**Table of CHAT Subcommittees**

<b>Committee</b>	<b>Members</b>	<b>Purpose</b>
<b>Neuropsych (NP)</b> Chair: Giordani with a separate call for Psychometricians	Core Director(s), clinical site Neuropsychologist, DCC  Psychometricians, DCC	Oversee psychometricians; training, conduction of study and scoring of instruments. Quality Control of NP data. Discuss and share tips on conducting testing
<b>Polysomnography (PSG)</b> Chair: Scott	Reading Center Director, sleep lab/clinic managers, DCC	Oversee equipment and data transfer from sites and adherence to protocol. Notify site coordinator of urgent alerts, data collection and transfer issues. PSG Quality Control.
<b>Publications</b> Chairs: Ellenberg, Redline	Project PIs, Core Directors, NHLBI, DCC	Develop publishing guidelines, coordinate publication data/materials between cores and clinical sites.
<b>Recruitment, Operations and Retention (ROAR)</b> Chair: Karamessinis, Co-Chairs: Amin, Rosen	Representation from 2 clinical PIs, research coordinators, DCC project manager	Monitor and discuss recruitment and retention issues. Track progress, share ideas, modify recruitment strategy, when applicable,
<b>Surgery</b> Chair: Garetz	Core Director, Site Co-PIs (surgeons) and DCC	Oversee AT surgery, tonsillar photographs and data quality.

## Participant Population and Recruitment

This study will involve participation of children and their caregivers. Female and male children, ages 5.00-9.99 years of age with documented Obstructive Sleep Apnea Syndrome (OSAS) will be recruited for this study. Documentation can be obtained from the medical chart and/or:

- 1) Obstructive Apnea Index (OAI)  $\geq 1$  or Apnea Hypopnea Index (AHI)  $\geq 2$ , confirmed on nocturnal, laboratory-based PSG (diagnosed by screening PSG exam or from existing PSG (done within the prior 60 days that has been sent to the reading center and rescored (refer to PSG MOP for details).
- 2) Parental report of habitual snoring (on average occurring  $>3$  nights per week).

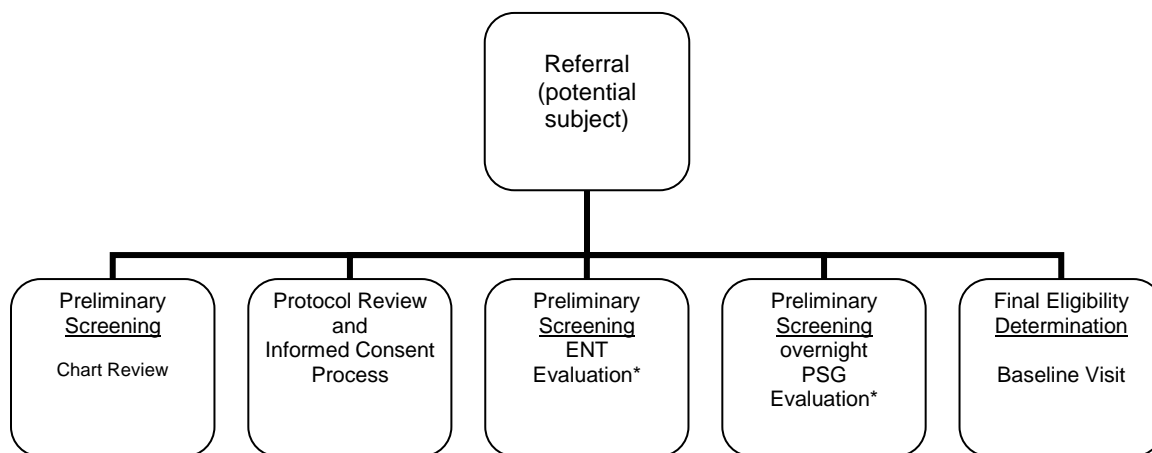
At every site, recruitment procedures must meet local HIPPA and IRB requirements.

### Sources of Referral

There will be several sources of referrals (a sample is demonstrated below)

Source	% Referrals			
	Cleveland	CHOP	Louisville	Cincinnati
ENT clinics	95	90	0	95
Sleep clinics	5	5	100	5
Sleep laboratory	0	5	0	0

Research personnel at each site will identify subjects who are potentially eligible. Children referred for evaluation of snoring or suspected OSAS at collaborating ENT practices and from the participating sleep clinics may go through several stages of screening. The order of screening evaluations may vary from site to site. CHAT protocol review and the informed consent process may occur at the time of another clinical visit (such as ENT) at the discretion of the family and site personnel.



\* ENT/PSG Evaluations may occur in opposite order depending on the site's initial referral source.

### Recruitment Procedures/Preliminary Eligibility Considerations

Procedures at each site will be implemented to identify potential subjects at some or all stages of the referral procedure. The procedures consist of regular review of electronic records and/or medical charts according to the site's institutional policy and HIPPA guidelines.

Once potential subjects are preliminarily identified the following procedures will be followed and may vary from site to site:

1. To enhance awareness about the CHAT study, IRB approved protocol-specific materials which consist of a brochure, advertising scripts or posters and an optional DVD will be distributed to potentially eligible subjects and their families. These materials can be mailed or provided to families during a clinic visit.
2. For children, a handout entitled: Picture Book About the CHAT Research Study (located in the Educational Materials Binder distributed during training or sent electronically) may be utilized to ascertain interest and describe procedures (must be approved by local IRB).
3. Families of potentially eligible subjects will be contacted about the CHAT study by telephone or during a clinic visit. Each site will utilize its own phone script to invite families and subjects to consider enrollment in the study.
4. The Preliminary Eligibility Worksheet (Appendix J) or the Child Information Worksheet [CIW] (available through the Data Management System) may be utilized to assist sites in tracking potentially eligible participants through the screening process. The forms should be retained in a separate "screening file" for those who are not eligible and stored in a secure location.
5. If families express an interest, a research visit will be scheduled for review of the protocol and informed consent. At the site's discretion, this visit may be combined with other clinical visits such as ENT or PSG when applicable.
6. Preliminary screening evaluations cannot be conducted until the Informed Consent has been obtained. These include an initial ENT evaluation to determine surgical candidacy and tonsillar size and a research PSG to determine OSA eligibility. *If an existing PSG and/or ENT evaluation exists, refer to item 7 below.* Detailed instructions on these procedures are listed in the specialty manuals attached; Appendix F: PSG Manual of Procedures and Appendix G: Surgical Quality Control Core (SQCC) Manual of Procedures.

## **Existing ENT and PSG Evaluations**

### **ENT (within the prior 90 days)**

If an evaluation was completed within the previous 90 days it may be used to determine eligibility. The unblinded research coordinator is responsible for extracting the information from the medical chart using the [PREOP] form (available in the DMS). The completed form will become the (study file) source document and must list the initials of the otolaryngologist who performed the exam, followed by the unblinded research coordinator's initials and date of transcription. The completed PREOP form will be entered into the DMS.

### **PSG (within the prior 60 days)**

Most children recruited from sleep labs/clinics will have undergone baseline PSGs at the participating clinic sites, following techniques that assure standardized data collection (i.e., sites will modify their routine procedures to use a standardized PSG montage, comparable sensors, minimal sampling rates, and filter use.) If the clinical PSG has been conducted within the previous 60 days, it must be sent to the PSG Reading Center (PRC) for re-scoring. Sites will be notified of PSG eligibility as described in Appendix F. *If a clinical PSG is on file that is more than 60 days old or was not performed using the research sensors and montage, as outlined in the PSG Manual, a research PSG must be scheduled.*

**NOTE:** A child who has PSG data that does not meet AHI/saturation criteria after central review is ineligible for the clinical trial, regardless of the local clinical interpretation of the PSG data. Once preliminary eligibility has been determined, families will be contacted, consent will be re-affirmed, and the fasting morning baseline exam will be scheduled.

## **Recruitment and Retention**

Successful recruitment and retention is critical for the success of this trial. Each of the clinical Principal Investigators (PI) has a recruitment goal of approximately 2-4 per month. The Executive, Steering Committees and Data Safety and Monitoring Board will closely monitor recruitment activities and address shortfalls if applicable, to determine issues that may be site specific. Recruitment data will be monitored by the DCC on an ongoing basis in order to assess recruitment rates at each site and to monitor deviations from projections. Each clinical center is responsible for determining how best to recruit participants from its local population. Other recruitment methods are described below.

### **Investigators Own Clinical Practice**

Many potential participants can and will be identified simply by considering the current participant population at the investigator's practice. The success of this method depends largely on the number of participants who are potentially eligible and interested in the study. When considering this as the main source of recruitment, investigators should not only evaluate how many participants will meet the study criteria, but also what percentage will be willing to participate in and comply with the study protocol.

### **Referral from Medical Practices of Other Physicians**

In order to facilitate participation from multiple referral sources (ENT, Sleep Lab or Sleep Clinic), the PI at each site must maintain contact with his/her colleagues, including the otolaryngologist who is the co-principal investigator at their site. Access to patients in large sleep referral centers and excellent relationships with ENT colleagues will facilitate research responsiveness (or equipoise).

It is also likely that each clinical center will need to rely on the referral of potential participants from the medical practices of other pediatricians to supplement enrollment from their own practice. In order to succeed, this method of recruitment requires the support of colleagues more than any other method. If potential referring physicians are not advocates of the study the number of referrals will be minimal, and the method not reliable for recruiting participants.

### **Recruitment Materials for Potential Participants**

Clinical centers are encouraged to prepare and utilize their own materials for the purpose of recruiting. Suggested CHAT-related materials were developed by the Recruitment and Retention Sub Committee and were provided electronically for site-specific modifications. Recruitment materials include brochures, flyers, or advertisements that can be used in a variety of settings (e.g. clinics, sleep lab, educational or promotional events) and/or may be mailed to families of potentially eligible participants. The material should be designed to describe the trial and participant study requirements as simply but accurately as possible and should include the name and contact number of the research coordinator (RC) or physician's contact information. Any recruitment material designed with the purpose of circulating to potential participants and his/her family must be approved by your local IRB prior to use, with a copy of the approved material sent to the DCC.

## **Recruitment, Operations and Retention**

### **Recruitment Tracking**

The Recruitment, Operations and Retention Subcommittee is chaired by Laurie Karamessinis, (Philadelphia) and co-chaired by Raouf Amin (Cincinnati) and Carol Rosen (Cleveland). Its members include the Research Coordinators from each clinical site, the project management



from the DCC and a representative from the NHLBI. The subcommittee oversees recruitment efforts, shares data about upcoming scheduled visits (such as screening PSG and baseline

visits), addresses operational issues and lend support to each other related to procedural concerns that arise. Conference calls are scheduled at least monthly to discuss recruitment challenges and to share strategies. Preliminary screening and recruitment efforts are monitored on bi-weekly basis, utilizing the Prescreening and Screening Summary Form [PSSF] which was designed following the guidelines listed in the Consolidated Standards of Reporting Trials Statement [CONSORT], (Jama, April 18, 2001-Vol. 285, No.15 pgs 1987-1991). These data will be collected and entered into the Data Management System (DMS) under the:

- Prescreening and Screening Summary Form [PSSF] by end of business day every other Friday (scheduled provided to coordinator electronically and is listed in Appendix I)

Reports will be generated to track recruitment efforts regardless of the participants eligibility status (participant does not have to be randomized to enter these data).

This report will be officially reviewed by the Steering Committee on a monthly basis and more frequently if recruitment milestones are lagging behind.

As necessary, the recruitment sub committee may request data that is not captured on the PSSF CRF and in those cases, an excel spread sheet (electronic template will be sent to each site) utilized for data collection. This template may be used as a worksheet to assist sites in tracking their own recruitment efforts and to aid in identification of recruitment challenges. This form will not be entered into the Data Management System.

### **Retention**

During the screening phase of the study, multiple alternative contacts (names and phone numbers) will be collected utilizing the Participant Contact Information Form [PTCON], obtained through the DMS. This will provide a means to get in touch with a participant when the main contact information fails. The RC will also maintain contact with the family approximately every 2 months via phone, in-between clinical visits. The Recruitment and Retention Subcommittee will also oversee the use of incentives (monetary and small gifts such as water bottles) to enhance retention.

## **Pre-Screening Contact and Data Collection**

### **Initial Contact with Family**

The first contact with a potential participant and his/her parent(s) or legal guardian will be considered a pre-screening contact and will include an introduction to the study, a review of the eligibility criteria, a description of tests and procedures involved, and a review of the visit schedule. This should be done to ensure not only the participant's *preliminary* eligibility, but also his/her willingness and ability to meet the demands/responsibilities of the study.

Pre-screening may be conducted either over the phone or in the clinic according to institutional guidelines. If the initial contact is by phone, the RC placing the call should identify him/herself and inform the family how they were selected. The RC should provide information about the study and answer questions. The **exclusion** and **deferral** criteria may be reviewed in order to reduce the number of potential participants scheduled for the PSG and Baseline Visits. If pre-screening determines that the potential participant is eligible and willing, the RC should schedule a time to review and complete the informed consent and schedule the first preliminary evaluation (ENT and/or overnight PSG).

## Preliminary Data Collection Forms (Tools)

An Administrative Form, the Child Information Worksheet [CIW] can be printed from the DMS and utilized to track participants through the screening process. Another 1-page tool can be found in Appendix J, the Preliminary Eligibility Determination Checklist. These forms are not entered into the data management system and are for administrative purposes. All data forms collected throughout the recruitment phase must be retained at the clinical site in a secure location.

## Informed Consent

### Overview

Each clinical center is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB), and State Department of Health requirements. The DCC provides a Template Consent Form with every protocol. The template language undergoes reviews by the DCC, Executive Committee and DSMB before being placed into the protocol. Each clinical center should use the template consent language as the basis for preparing their consent as per local IRB guidelines. The DCC must approve all local consents to ensure their consistency with the template language as well as ICH guidelines prior to being submitted to the IRB. Each site must also forward a copy of their local consent to the DCC once it receives IRB approval. The informed consent form must be obtained (signed and dated by the participant) **prior** to initiation of any study related activity. Specifically, the following must be accomplished during the informed consent process:

- The participant/parents/legal guardian must be informed that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits.
- The participant/parent/legal guardian must be informed that the study involves research.
- The participant/parent/legal guardian must be informed of any alternative procedures.
- The participant/parent/legal guardian must be informed of any reasonable foreseeable risks.
- The participant/parent/legal guardian must be informed of any benefits from the research.
- An outline of safeguards to protect participant's confidentiality must be included, as well as an indication of which parties are allowed to review the record.
- The participant/parent/legal guardian's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if they decide to enroll.
- The participant/parent/legal guardian must be informed of his/her right to have questions answered at any time. The RC should allow the potential participant time to consider the study obligations and discuss the study with his/her family members before signing the consent form.
- The informed consent form must be signed in the presence of the PI or the RC, prior to collection of any study-related data or blood specimens are performance of study procedures.

An informed consent must be obtained from the participant/parent/legal guardian before any study-related data are collected and study procedures are performed. In the case of PSG and ENT screening, existing evaluations may be utilized to determine eligibility according to the guidelines listed in item 6 above.

## Administration of Informed Consent

The participant is screened to confirm his/her eligibility by reviewing the inclusion, exclusion and deferral criteria with his/her parent/legal guardian. Once deemed eligible, the coordinator will provide the potential participant's parent or legal guardian with a copy of the Informed Consent Form and ask the participant and/or parent/legal guardian to read a few sentences out loud to ascertain whether the potential participant and/or parent/legal guardian need assistance with the written material. After the participant and/or parent/legal guardian has had a chance to ask questions, the consent form must be signed and dated.

The informed consent form should be reviewed in a comfortable setting where the participant/parent/legal guardian is able to make a free choice without pressure. Ample time should be given to allow the participant/parent/legal guardian to thoroughly read, process the information, and ask questions. If the family wishes to take the Informed Consent home before reaching a decision, they may do so. At the subsequent visit, the coordinator and/or principal investigator should answer any questions raised by the participant and h/her parent or legal guardian.

The participant/parent/legal guardian should be made aware of their responsibilities throughout the Screening process, during the baseline visit, after the randomization assignment is known and throughout the study period. The importance of continued follow-up should be stressed and balanced with a discussion of the effect of participant withdrawal on the study.

The Informed Consent Form **must** be signed and **personally** dated by the participant's parent or legal guardian, and by the person "obtaining consent". A participant's parent/legal guardian should not be asked to sign the consent statement if s/he has any doubts about enrolling their child or if the clinical staff believes s/he does not understand what participation would involve. Under *no* circumstance is any study information to be collected or study procedures performed for the specific purpose of the trial **before** the participant's parent or legal guardian has signed the informed consent form.

The RC will maintain the original consent document in the participant's confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the parent/legal guardian who should be urged to retain the document for future reference. A second copy of all informed consent(s) should be made as a back up and stored together in the "study-confidential file". In addition, the informed consent process must be documented on a progress note or similar form as designated by your institution, signed/dated and maintained in the participant's file.

To ensure confidentiality, the RC will not send copies of the informed consent form(s) signed by the participant/parent/legal guardian to the DCC or specialty core groups and must keep copies of the informed consent form with the case report forms (CRFs).

## Attestation

In addition to the Informed Consent children ages  $\geq 7$  must sign an Attestation Form if required by your IRB.

## Teacher Authorization Form

At the time of the informed consent process, an authorization form allowing the child's teacher to release information may be reviewed and signed by the parent/legal guardian. The signed authorization will be sent to the child's teacher according to the directions outlined in Appendix E: NP Manual of Procedures A template of an authorization form and Teacher Questionnaire are listed in Appendix H: Supplemental Materials.

## Authorization to Release Medical Information

During the initial contact with the child/parent/legal guardian the site may request that a general authorization to Release Medical Information form be signed by the parent/legal guardian for permission to obtain medical records from physicians/clinics unassociated with the study. This form is site specific and is utilized according to local institutional guidelines.

### Important information about Parent/Legal Guardian Signature

It is important to note that the child's parent and/or legal guardian must sign the informed consent. No other family member or accompanying adult is authorized to do so.

However, it is understandable that there may be times when an adult other than the child's parent/legal guardian may accompany the participant to study visits.

For consistency in data quality, every attempt must be made to collect information from the parent/legal guardian who signed the consent form whenever possible throughout the study.

## Confidentiality

### Assignment of Participant ID

Once the participant/parent/legal guardian has signed the informed consent, the participant will be assigned a Participant Identification (PID) number from the [PTLOG]. This log is an administrative form developed in advance by the DCC for each clinical center. The form includes a column with hard coded participant ID numbers and a blank column for participant initials.

The PID is a 6-digit number that is a unique identifier for each study participant and will only be used once regardless of participant status (screen failure, enrolled, lost to follow up, withdraw, etc.). Each PID begins with the 2 digit site number followed by a 4 digit participant number (refer to sample log below).

- 10 (CHOP)    xxxx
- 20 (CINN)    xxxx
- 30 (CLD)    xxxx
- 40 (LVL)    XXXX (as of 10.4.08 no longer recruiting)
- 50 (SLU)    xxxx
- 60 (MNYC)    xxxx
- 70 (BOST)    xxxx

An alphabetic code representing the initials from the participant's first, middle and last name will also be used as an additional identifier for quality control purposes. If the child does not have a middle initial or if it is not known, the letter "X" should be used in that field.

Each participant should be assigned the next available Participant ID number.

All communication regarding individual participants must be through the Participant ID number and your clinical center code. Once a Participant ID number has been assigned, it should never for any reason, be reassigned. The [PTLOG] form should be stored in a secure, locked filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location.

Participant ID Assignment Log Example (CHOP site 10 is used in this example)

PID (hard coded by DCC)	Child's Name (First, Middle, Last)	Initials	Date Consent Signed	RC – ID (assigned by DCC)
101001	Jonathon J Doe	<u>J J D</u>	___ / ___ / _____	___ - ___
101002	Kimberly <b>X</b> Lacy (in this example the participant does not have a middle initial and an <b>X</b> is placed in that field)	<u>K <b>X</b> L</u>	___ / ___ / _____	___ - ___
101003	Terry D Church	<u>T D C</u>	___ / ___ / _____	___ - ___

## General Information

Extensive efforts will be made to ensure and maintain participant confidentiality, except as may be required by law and/or institutional regulations. All identifying information **must** be maintained in a secure area at all times and **must never** appear on CRFs. Consent form(s) and source documentation **must** be maintained in a separate folder from the CRFs. If source documentation has to be made available for data audits, copies of the source documents should be forwarded to the DCC with only Participant ID number visible and personal information obscured.

The DCC staff has access to the *Participant ID* number for data management purposes. All communication between the DCC staff and the clinical center staff regarding participant data occurs via the *Participant ID* number only. All CRFs and source documents sent to the DCC **must** have all participant identifiers, other than the *Participant ID* number, obscured. However, please never obscure information on the original/source documents. The staff at the DCC **will not** have access to any participant locator or identifying information available to the clinical center.

## Eligibility Criteria

Participants must be diagnosed with Obstructive Sleep Apnea Syndrome (OSAS) according to the definition described on item 2 of the inclusion criteria listed below and will be determined during the screening PSG.

## Inclusion Criteria

Children with Obstructive Sleep Apnea Syndrome or OSAS usually snore loudly and have total or partial upper airway obstructions that repeatedly interrupt sleep. CHAT-defined inclusion criteria are:

1. Ages 5.0 to 9.99 years at time of screening
2. Diagnosed with Obstructive Sleep Apnea defined as:
  - Obstructive Apnea Index (OAI)  $\geq 1$  or Apnea Hypopnea Index (AHI)  $\geq 2$ , confirmed on nocturnal, laboratory-based PSG *and*
  - Parental report of habitual snoring (on average occurring  $>3$  nights per week).
3. Tonsillar hypertrophy  $\geq 1$  based on a standardized scale of 0-4:
  - 0 = surgically absent
  - 1 + = taking up  $< 25\%$  of the airway
  - 2 + = taking up 26 – 50 % of the airway
  - 3 + = taking up 51 – 75 % of the airway
  - 4 =  $> 75\%$  of the airway
4. Deemed to be a surgical candidate for AT by ENT evaluation

## Exclusion Criteria

1. Recurrent tonsillitis that meets published ENT clinical practice guidelines for surgery defined as:  $\geq 3$  episodes in each of 3 years, 5 episodes in each of 2 years, or 7 episodes in one year.
2. Craniofacial anomalies, including cleft lip and palate or sub-mucosal cleft palate or any anatomic or systemic condition which would interfere with general anesthesia or removal of tonsils and adenoid tissue in the standard fashion.
3. Obstructive breathing while awake that merits prompt AT in the opinion of the child's physician.
4. Severe OSAS or significant hypoxemia requiring immediate AT as defined by:
  - OAI  $> 20$  or
  - AHI  $> 30$ ,
  - Desaturation defined as SaO<sub>2</sub>  $<90\%$  for more than 2% sleep time
5. Apnea hypopnea indices in the normal range (OAI  $<1$  and AHI  $<2$ )
- 6 Evidence of clinically significant cardiac arrhythmia on PSG:
  - Non-sustained ventricular tachycardia
  - Atrial fibrillation

- Second degree AV block
    - Sustained bradycardia < 40 bpm (> 2 minutes)
    - Sustained tachycardia > 140 bpm (> 2 minutes)
7. Extremely overweight defined as: body mass index > 2.99 age group and sex-z-score (refer to CDC charts for body mass index-for-age percentiles in (Appendix I: Shadow Documents).
  8. Severe health problems that could be exacerbated by delayed treatment for OSAS Including:
    - Doctor-diagnosed heart disease or cor pulmonale
    - History of Stage II Hypertension (HTN) defined as > 99% percentile (CDC prediction equations) plus 5 mmHg for either systolic or diastolic examination, based on the age, gender, and height and/or requiring medication.

*Note:* If Stage II HTN is noted upon examination, or at the PSG, patients will be referred for follow-up with their pediatrician. The Urgent Medical Referral Form (UMRF) listed in Appendix H: Supplemental Materials must be completed and faxed to the pediatrician's office, where BP is advised to be measured on at least two more occasions. If subsequent evaluation proves BP to be less than Stage II, then the patient may be referred for re-evaluation for entry to the CHAT study.

    - Therapy for failure to thrive or short stature
    - Psychiatric or behavioral disorders requiring or likely to require initiation of new medication, therapy, or other specific treatment during the 7month trial period.
    - For school aged children, parental report of excessive daytime sleepiness defined as unable to maintain wakefulness, at least three times per week, in routine activities in school or home, despite adequate opportunity to sleep.
  9. Severe chronic health conditions that might hamper participation including:
    - severe cardiopulmonary disorders (e.g. cystic fibrosis, congenital heart disease)
    - sickle cell anemia
    - poorly controlled asthma (with >1 hospitalization in last year)
    - epilepsy requiring medication
    - diabetes (type I or type II) requiring medication
    - conditions likely to preclude accurate polysomnography (e.g. severe uncontrolled pain)
    - mental retardation or enrollment in a formal school Individual Educational Plan (IEP) and assigned to a self-contained classroom for all academic subjects
    - history of inability to complete cognitive testing and/or score on DAS II of  $\leq 55$
    - chronic infection or HIV
  10. Known genetic, craniofacial, neurological or psychiatric conditions likely to affect the airway, cognition, or behavior
  11. Current use of one or more of the following medications (Appendix I: Shadow Documents: List of exclusionary medications by name)
    - ADHD medications

- psychotropic medications (antidepressants, anxiolytics, antipsychotics)
  - hypnotics
  - hypoglycemic agents or insulin
  - antihypertensives
  - growth hormone
  - anticonvulsants
  - anti-coagulants
  - daily oral corticosteroids
  - daily medications for pain
12. Previous upper airway surgery on the nose, pharynx or larynx), *Note:* Ear surgery and/or PE tubes or prior adenoidectomy are not exclusion criteria.
  13. Receives Continuous Positive Airway Pressure (CPAP) treatment
  14. A parent or guardian who cannot accompany the child on the night of PSG
  15. A family planning to move out of the area within the year
  16. **Female participants only:** Parental report that child has reached menarche.

## Deferral Criteria

There may be some situations or conditions for which a participant will be deferred from entry into the study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the study. Some of the criteria are listed below:

### Conditions for Deferral

1. Subjects currently enrolled in another intervention or longitudinal study.
2. Subjects who have received an investigational drug or device within 30 days prior to screening will be deferred until off study for a period of at least 30 days.
3. Child and parent/guardian request additional time to consider treatment options.
4. Child found to meet criteria for Stage II hypertension at the PSG or baseline visit. If subsequent clinical evaluation conducted within 30 days of initial finding indicates repeated blood pressure levels do not meet or exceed Stage II criteria and/or they are not prescribed antihypertensive medications as defined in the inclusion criteria, the child may be re-evaluated for study entry.
5. Child currently on a “burst” of oral corticosteroid therapy. Participant may be re-evaluated once daily oral corticosteroids are no longer prescribed and 30 days have passed since the last dose.

Some parents/legal guardians may be poor historians and/or have a limited understanding of their child's health problems and associated treatments. For those questions which are denoted in your records as reported by the “child's parent/legal guardian”, it is advisable that the response be verified with a medical record/report whenever possible.

If the participant is deferred for any of the reasons listed above each site may want to design and maintain their own deferral log for tracking purposes. The deferral log is an administrative tool and will not be entered into the DMS.



To determine the re-screening date for a participant who has been deferred for more than one criterion, the coordinator will select one date that allows sufficient time for all deferral criteria to have been resolved. The coordinator should contact the family by telephone close to the ending date of the deferral period which in most cases will not be more than 30 days to:

- Review the study with the family
- Determine whether the deferral condition is resolved if applicable
- Ascertain if the participant/parent/legal guardian is still interested

## Screen Failures

A participant who *has signed the informed consent* and does not complete the screening procedures for whatever reason will be considered a screening failure and will not be randomized to the trial. For example, a participant who completes the ENT evaluation and does not return for the PSG visit will be considered a screening failure.

This does not include children who are unable to complete the blood draw during the baseline visit despite efforts by parent/legal guardian, research coordinator and Principal Investigator.

Potential participants who do not meet one or more of the following criteria are considered *screen failures* and will not be enrolled (randomized) into the study:

### Criteria

- Not suitable for surgery or delay in surgery as determined by ENT
- Overnight sleep time in desaturation of < 90% for > 2% of sleep time, OAI >20 or AHI >30
- Inability to complete cognitive testing
- DAS-II score of ≤ 55 on summary IQ
- Confirmed Stage 2 Hypertension (> 99% for age and gender)

Screen failures can occur during any stage of the preliminary screening process (ENT, PSG evaluations and/or at the baseline visit) *after* the informed consent has been signed and at least one or any combination of the criteria defined above has occurred. A **Study Stop CRF [SSTOP]** must be completed and entered into the DMS to indicate that the child has failed screening. All of the completed screening forms, including the informed consent should be filed at the clinical site in the Source Documentation Binder and should not be sent to the DCC. The study visits completed up until the point of failure prior to randomization must be entered into the DMS. Also, completion of the following forms is required to track reasons for screen failures and generate reports:

### Additional forms to complete for Screen Failures

1. The Prescreening and Screening Summary form (PSSF) lists screening activity totals (no individual information) and is entered on a biweekly basis.
2. SSTOP (individual participant information) is required for each child who fails screening (ENT, PSG, Baseline, etc.) and *who has not been randomized*.

Sites should maintain a prescreening file/log to record and/or maintain preliminary screening records.

## Entering Pre-Randomization Data into the DMS

Prior to randomization (during the screening phase of the trial), data may be collected by the clinical center's CHAT trained personnel. It is suggested that each site designate one person as the data management system "expert" for CHAT. This person (preferably the unblinded research coordinator) must be trained and certified on the use of the Data Management System and will be responsible for training new personnel as needed with assistance from the DCC.

Access to the data management system will not be granted until the training module has been completed and the individual has been certified.

### Access to Database

To protect the integrity of the study design related to blinding, access to the database is limited to the unblinded research coordinator and designated data entry personnel or research assistants. *Note:* The blinded research coordinator may assist in entering data as dictated by the site's lead (unblinded) coordinator (e.g. NP data, for example).

User ID/passwords should only be utilized by the person for whom they were assigned. Under no circumstances should personnel IDs and passwords be given out or posted in non secure areas or files. This insures quality data entry and tracking, avoids accidental breaching of the treatment arm assignment by blinded personnel and maintains the integrity of the data and study design. Refer to the DMS Users Guide for complete details.

The majority of the screening data will be known and/or collected by the time of the baseline visit and may be entered into the DMS prior to baseline, if applicable. However, the following exclusionary criteria may not be known until the baseline neuropsychological testing has been completed:

- Child is found to be unable to complete cognitive testing
- DAS-II score is < 55 on IQ summary

In these cases, the child will not be eligible and the CHAT-trained neuropsychologist and/or psychometrician will notify the coordinator at the time of the visit. The family will be informed of the outcome and referred for follow up testing as recommended by the neuropsychologist. Refer to Appendix E: Neuropsychological (NP) Manual of Procedures for details.

## Randomization

Only participants who have *successfully* completed the entire screening process through the end of the baseline visit will be randomized.

The following items will be assessed to confirm eligibility:

- The inclusion and exclusion criteria will be reviewed and checked against the Eligibility Confirmation CRF [**ELIG**], including the ENT and PSG evaluations and neuropsychological summary score of DAS-II.

The DMS is designed to prevent ineligible participants from being randomized. If the eligibility data for a participant proves a participant is **ineligible**, the DMS will **not** allow data entry. If the data entered are consistent with the requirements for randomization into the study the **site-designated unblinded coordinator** will be the only person who has authorization to access the randomization data base. The unblinded coordinator must complete the Randomization [**RAND**]

form and enter it into the DMS to receive the computer-generated randomization code. The randomization code will not be assigned until all the questions have been answered and automatically crosschecked in the system with previously entered data. After the DMS provides the code, the unblinded coordinator will enter it on the [RAND] form.

The randomization process is an administrative task that occurs after all the screening and selected baseline data (i.e., those required to determine eligibility) have been collected and entered into the DMS. The *unblinded* research coordinator may randomize the subject at the end of the baseline visit while the family remains in the clinic (ideal) or within 48 hours of the baseline visit. If the participant is not randomized at the end of the baseline visit, an interim phone call to query the parent/legal guardian must be made to verify that no Adverse Events or changes in medications have occurred.

### **Confidentiality of Randomization Code(s)**

In order to maintain the integrity and blinding of the study arm assignment, the completed [RAND] form must be kept in a separate location that only the unblinded coordinator has access to. All attempts to keep this code confidential must be made. Only the unblinded coordinator should see this information.

### **Maintaining Study Blind**

In order to minimize biases related to unblinding of investigators, psychometricians, PSG technicians and other study personnel (research assistants), only the unblinded research coordinator and ENT surgeons will have knowledge of the treatment arm assignment. All efforts will be made to keep CHAT study personnel involved with primary data collection blinded to the treatment group. The unblinded coordinator will instruct the child/parent/legal guardian and/or family members not to discuss any aspects of their treatment with the psychometricians and PIs performing the tests/assessments during the follow up visits at months 3 and 7. The family will also be reminded not to discuss the treatment assignment with the PSG technicians during the 6 month polysomnography visit. All phone visits should be conducted by the unblinded coordinator to avoid unnecessary breaching of the study arm assignment.

The unblinded research coordinator will direct all study-related correspondence to h/her attention and instruct the family to contact h/her directly about all study-related and/or medical concerns throughout the course of the trial.

However, it may be possible that the code or treatment arm will be divulged during testing/clinical visits to study personnel who are blinded. Any such instance of this will be recorded.

There may be cases when the treatment arm assignment may have to be unmasked (e.g. patient safety). In these cases, the unblinded coordinator must complete the Unblinding [UNBLIND] CRF according to the instructions listed in Appendix I.

### **Unblinded Research Coordinator's Role in Maintaining the Blind**

In order to maintain the study blind and the validity and integrity of the data, while, at the same time ensuring the safety of participants, the unblinded coordinator must oversee and monitor the child's study-related records. It is the unblinded coordinator's responsibility to place these files in a secure location and to distribute the case report forms to blinded study personnel separate from the child's source documents, when applicable.

To safe guard against the accidental breach of treatment arm assignment post randomization, the unblinded coordinator's primary responsibilities include:

- Notifying child/parent/legal guardian of treatment arm assignment and reaffirming consent

- Acting as liaison between child/parent/legal guardian and other clinical or specialty core departments when applicable
- Notifying families of visits and keeping track of the schedule
- Scheduling initial ENT Evaluation, Overnight PSGs when applicable (in most cases)
- Obtaining PSG Results from the Reading Center's FTP Server and following up on Urgent Alerts
- Scheduling AT surgery and ENT re-evaluation visit and coordinating intraoperative photos
- Conducting clinical visits and/or assuring that only CHAT-certified personnel perform the procedural elements required during those visits (anthropometry, resting BP, etc.)
- Collecting or overseeing blood collection, processing, storage and shipping of samples.
- Coordinating AT data collection (including photos) with ENT
- Distributing data collection/case report forms to study personnel when indicated (Pre-Operative questionnaire [Pre-Op] for ENT evaluation and NP Summary Forms, for example)
- Acting as the primary contact for participant's study-related/medical concerns
- Monitoring patient safety and SAE reporting; notifying the Medical Monitor and DCC accordingly
- Tracking and Reporting Potential Treatment Failures (PTF) to the Medical Monitor and DCC.
- Delegating other study-related tasks to blinded personnel (including data entry) when indicated
- Conducting phone visits
- Entering "**blinded**" data (e.g. surgery, AEs and Concomitant Medications, etc.)

### **Back-up Personnel**

Site personnel unassociated with the trial may have knowledge of the study-file(s) location and/or keys to access the information for safety purposes in the absence of the unblinded coordinator. This person should not be involved with CHAT data collection and must be listed in the CHAT directory as a back up contact for the site (administrative assistant for example).

### **Back up Manual Randomization**

In the event of a computer failure at one of the Clinical Centers and / or the DCC during randomization, the unblinded Research Coordinator will call the DCC during the hours of 9:00 am to 5:00 pm (Eastern Time Zone), Monday through Friday at one of the following numbers:

**215.573.8195 – Terry Church**

**215.573.0172 – Kim Lacy**

**215.573.4623 – Helpdesk**

If no one is available, leave a detailed message and a member of the DCC CHAT study team will return the phone call and ask that the unblinded RC fax the following Case Report Forms (CRFs) for the participant(s) the site is attempting to randomize: Pre-Operative Questionnaire [**PREOP**], Protocol Defined Eligibility [**ELIG**], and Randomization [**RAND**]. This data will be reviewed verbally with the unblinded RC, who will also be asked what portions – if any – of this

data has been entered. The unblinded RC will also be asked about the randomization assignment of the most recently randomized participant (the last randomization code number assigned).

After the DCC representative confirms the participant's eligibility, the DCC representative will assign the next available randomization assignment. The DCC representative will confirm the randomization number generated electronically with the manually assigned number, and instruct the sites how to proceed with entry.

The RC will fax copies of the CRFs needed for manual randomization and manual audit at the DCC. A manual audit will facilitate a visual check data of the faxed CRFs against data provided during the phone call.

If the unblinded RC was not able to randomize due to computer failure at their site, they should verify with the DCC that the database has been updated since the telephone randomization was performed after their system has been restored to normal working order, prior to entering data on new participants. If the unblinded RC was not able to randomize due to computer connectivity problems with the CRCU interface, the DCC representatives will notify the RC when the data management system (DMS) is operational again.

### **Participant Visit Schedule**

The data management system will generate a visit schedule at the time of randomization. The visit schedule is generated based upon the randomization code and therefore only the unblinded coordinator will have the authority to view and print it. The schedule must be maintained in a secure location to assure blinding. The unblinded coordinator will provide the family with a copy and utilize it as a tool for tracking purposes.

### **Participant Withdrawal and Withdrawal of Consent**

Participants are free to withdrawal (or be withdrawn) from the study at any time. The various reasons for withdrawal may include:

#### **Reasons for Withdrawal**

- Adverse Event/Serious Adverse Event
- Significant concurrent illness
- Protocol noncompliance
- Investigator's discretion
- Withdrawn informed consent
- Relocation
- Use of unacceptable concomitant medications
- Dissatisfaction with treatment
- Loss of interest in the study
- Lost to follow-up

Reason(s) for withdrawal will be documented on case report forms and recorded at the DCC. For those participants who withdraw (or are withdrawn) due to AE/SAE, the Adverse Event [AE] CRF must be completed.

#### **Voluntary Withdrawal**

If a participant indicates that they no longer wish to participate in the study (withdrawals consent), the RC will follow up with a formal letter (written on the institution's letterhead) for the

parent/legal guardian to sign. If this document is mailed to the family, it must be sent certified mail. The certified mail receipt should be kept with the participant's records. The letter should contain the following information:

*I voluntarily withdrawal my consent to participate in this study.*

- I no longer wish to be contacted by the clinic regarding this study.
- I understand that my records will be kept confidential.
- I can continue to receive my regular care and treatment at this clinic.

The coordinator will complete the Study Stop Point [**SSTOP**] form selecting the most representative reason for withdrawal.

The RC will also complete the Treatment Stop Point [**TSTOP**] form if the withdrawal occurs during the treatment phase. Every effort should be made to encourage participants to continue with study visits even if they stop treatment early, regardless of arm.

The withdrawal request can be made in person or during a phone contact. The participant's study chart (source file) must be clearly marked to indicate withdrawal and be maintained at the clinical center where the participant was recruited and followed. The DCC Project Manager is informed of the participant's withdrawal, so that the data archival process at the DCC can be initiated.

## Study Related Documents/CRFs/Administrative Forms

### Overview

The Data Management System (DMS) contains administrative logs, data entry forms, adverse event and concomitant medication CRFs in addition to other forms which can be accessed and printed prior to each visit. Individual participant visit packets should be printed out prior to the scheduled visit and must be completed before entry into the DMS. A Data Processing Coversheet will be provided in each visit packet listing the required forms for that visit.

### Administrative Forms

A complete description of these forms is listed in Appendix I: Case Report Forms.

### Neuropsychology (NP) Forms

The unblinded coordinator will distribute the NP forms (Baseline, Month 7 to the psychometrician for completion. note: *except in the case of determining eligibility (baseline DAS-II summary score), the psychometrician has up to 7 days to:*

- Score the exams following testing
- Complete and proof the CRFs
- Return the CRFs to the coordinator for entry into the DMS.

The following questionnaires are not available through the DMS:

- Parent Brief, Conners' Rating Scales and CBCL (Achenbach)
- Teacher Brief and Conners' Rating Scales.

These instruments are available for purchase according to the instructions listed in the NP Manual and should be available through the NP and/or Psychometrician at each site.

## Teacher Ratings/Questionnaires

Teacher questionnaires will be sent out to each child's *current* teacher (or prior year if during summer months) to complete and return at the baseline and Months 7 visits. These forms are not accessible in the DMS and should be available at each site for distribution (Brief and Conners' Teacher). Once it is determined that a participant is potentially eligible, and the baseline visit is scheduled, teacher-report questionnaires, a brief cover letter explaining their purpose, and a postage-paid return envelope will be mailed to the teacher, if the child is in school. It is allowable for the baseline teacher questionnaires to be mailed as early as the time of consent to maximize completion prior to any intervention, but such an early mailing may not always be possible, given the multiple recruitment sources and processes. Mailings should occur between 2-4 weeks prior to the 7month visit. Refer to Appendix H: Supplemental Materials for sample cover letter and questionnaires.

If a teacher questionnaire has not been returned by 1 week after a child's visit (baseline, month 7) the coordinator will call the teacher to inquire if he or she has any questions about the process or needs another packet.

As indicated in the cover letter, teacher return of questionnaires will be voluntary and will not affect a subject's participation in the study. To minimize missing data, teachers will receive a \$10 honorarium for returning questionnaires.

## Record Keeping

### Document Binders

Participant study documents must be made available to the specialty cores, Data Coordinating Center and the NHLBI when necessary for safety and quality control and/or as required by law for regulatory purposes. These documents should be organized in binders or files (outlined below) and stored in accordance to security and record retention regulations and until further written notice by the sponsor or the DCC. Each clinical center must maintain the following documents in binders/folders:

### Clinic Regulatory Binder (1 per clinical center)

This binder contains all essential documents, according to GCP guidelines, required for conducting a clinical trial:

- Protocol/Amendments and Signature Page(s)
- Informed Consent Form/Attestation/HIPPA
- IRB Correspondence
- IRB Membership List, if applicable (current for duration of trial)
- General Correspondence (DCC, NHLBI, Reading Center, etc.)
- Curriculum Vitae and License of all clinical personnel (current within 2 years)
- Signature and Delegation of Responsibilities Log [STAFFLOG]
- Adverse Events\*
- Site Monitoring Log
- Reports\*

*\*Note to file:* Documents outlined above may be stored in other/additional binders during the course of the study; however a “Note to File” should be placed in any section where this occurs as a means to track the document during a monitoring visit.

### **Master Manual of Procedures (1 per site)**

The Master Manual of Procedures contains operational instructions to carry out the study-specific procedures, the Data Management System Users Guide and manuals for each specialty core (located in the appendices). Specialty manuals act as stand alone documents and may be copied and maintained in the corresponding clinical area/unit as reference guides for CHAT-trained and certified personnel. The Specialty Manuals Include:

- Anthropometry (ANTHRO)
- Blood Pressure (Resting)
- Laboratory for Clinical Biochemical Research (LCBR)
- Neuropsychological (NP)
- Polysomnography (PSG)
- Surgical (SQCC)

Additional Appendices include:

- Supplemental Materials (such as teacher forms, etc.)
- Step-by-Step Case Report Forms with Instructions for Completion
- Tools (Reference Materials)

### **Case Report Form Binder (1 per study participant)**

This binder contains all data collection forms that have been entered into the DMS and select administrative forms completed during the course of the trial. No participant identifiers other than participant ID number and participant initials should be contained in this binder. Any information that could unintentionally reveal the study arm assignment should be maintained in a separate, secure location.

### **Source Documentation Binder (1 per study participant)**

Contains all documentation collected to support and verify information contained on the data collection forms. This includes the following original source documents: participant /parent/legal guardian signed informed consent, child’s attestation form if applicable, medical records, laboratory results, administrative forms not contained in the Case Report Form Binder such as the Participant Contact Information [PT CON] and the Child Information Worksheet [CIW], progress notes, and correspondence. In addition, any copies of applicable source documentation should also be stored in this file. Study documents that have participant identifiers beyond PID and participant initials should be contained in this file.

If blinded study personnel have access to the participant’s source file, Surgical CRFs/source documents must be maintained separately in a secure location for the purpose of protecting the integrity of the trial and maintaining the study blind. The unblinded coordinator and a site representative (not associated with CHAT) will have access to these files.

### **Participant Study Binder (1 per clinical center)**

This binder contains Participant ID Assignment Log [PTLOG] a copy of all participant signed informed consents and all financial documents related the study. Any additional study specific confidential documents should be contained in this file such as the prescreening form [PSSF].



It is suggested that each site implement a mechanism to track visit due dates for each child and record dates that the parent/child/family were contacted. This could be an individual “Participant Contact Log” that is designed to aid in tracking visits and to record [the site’s] date of or attempt at making contact. *The log may be kept in the study file as long as the surgical visits are tracked and kept in a different location.*

In addition, another log each site may want to consider is a Deferral Log that is designed to track participant/parent/legal guardians who are interested in participating but cannot participate until one or more of the criteria for deferral has resolved.

## Visit Scheduling and Administration: Screening/Baseline Phase

The Screening/Baseline phase may be up to 4 visits, depending on the site’s recruitment methods and the child/parent/legal guardian(s) circumstance and/or preference.

### Overview

#### Preliminary Identification of Potential Subjects

A chart review to determine initial eligibility may be conducted according to institutional HIPPA requirements prior to scheduling the screening evaluations or ascertaining interest. Sites may utilize the Child Information Worksheet [CIW] as an administrative tool designed to assist in the tracking the screening components.

The *Preliminary* Screening Phase of the study consists of the following evaluations which will be conducted as separately scheduled visits:

- Initial research clinical visit with child/parent/legal guardian to ascertain interest, review and obtain informed consent and obtain additional information (*may be combined with either of the visits listed below, if applicable*).
- Overnight PSG visit (unless a PSG has been conducted within the previous 30 days and sent to the Reading Center to be rescored).
- ENT clinical visit (unless an evaluation has been done within prior 90 days).

#### Preliminary Screening Components

A chart/medical record review of existing patients in your clinic(s) may assist in preliminary identification of potential participants at your site. These data must be reviewed in accordance with your institutional guidelines and HIPPA regulations. As stated above the CIW may be utilized to assist in this process.

*Preliminary* screening and eligibility determination consists of several evaluations that may require up to 3 visits depending on the source of the referral, the family circumstances and family or site’s preference. These visits occur prior to the baseline clinical visit and determine preliminary eligibility. The following information may apply:

- If at any time during the screening process the child is found to be ineligible, the child and h/her parent/legal guardian must be informed as soon as possible. If the reason is related to a clinical value discovered during the ENT examination or PSG testing the family will be referred back to their primary care provider or clinic for follow up evaluation.
- If the child appears eligible after a preliminary review of h/her medical record (if available) and/or if referred from the ENT clinic, then the family may be approached to find out if there is an interest.
- Once interest is established the informed consent process must take place prior to any study related data collection/testing.

- Potential participants must meet eligibility criteria from both the ENT evaluation and PSG testing before undergoing the baseline exam to determine final eligibility.
- If a potential participant is not scheduled for the baseline visit within 2 -4 weeks of the PSG exam or rescoring of an existing PSG exam, then the parent/legal guardian must be queried about changes to their child's medical status, signs and symptoms related to OSAS, medication changes, etc. The informed consent must be reviewed to reiterate the purpose of the trial and the study arm assignment.
- A child who is initially deferred from entry based on the deferral criteria may be reconsidered for inclusion at a later date, if the condition(s) **resolves** according to the specified time frame. A child previously **excluded** based on the exclusion criteria **cannot** be re-screened.
- The participant ID number will not be re-assigned for any reason.

***A Note about Preliminary Screening Visits:***

Regardless of the site's method of recruitment, from clinical/sleep lab or ENT, which ever comes first, there is a 60 day window to obtain all the screening visits/information (including the polysomnography and ENT evaluations prior to the baseline visit/randomization. *NOTE:* There may be cases when a prior ENT evaluation exists in the medical chart and the child has not yet had surgery. Existing evaluations can be utilized in the place of the clinical ENT appointment and in this case a 90 day window applies.

## **ENT Screening Visit (ENT)**

Initial contact with a potential subject and h/her parent/legal guardian may occur as a referral through the ENT clinic. Once interest in CHAT has been established, the participant will be evaluated by the otolaryngologist for surgical candidacy. The ENT performing the exam will complete the following form: Pre-operative Questionnaire [PREOP].

### **Existing ENT Evaluations**

If a potential candidate has an existing ENT evaluation on file (within the previous 90 days) it may be utilized to determine preliminary eligibility for surgical candidacy and tonsillar size. Refer to the Surgical Manual of Procedures for details related to the ENT visit, pre-operative evaluation and data collection. At the discretion of the family and study personnel, additional information may be collected during this visit. Forms that require review with the parent/legal guardian/child and signatures include:

- Informed Consent/Attestation (IRB approved Consent/Attestation)
- Teacher Authorization to Release Information Form (Appendix H: Supplemental Materials) if applicable
- Medical Release Authorization Form (institutional based)

If a separate visit is required to review the protocol and informed consent, the coordinator should schedule this as soon as possible (within one week).

## **Polysomnography [PSG] Pre-Study and Periodic PSG Equipment Verification**

Prior to initiation of a PSG on a potentially eligible candidate, all equipment must be CHAT-certified by the core Reading Center at Case Western following the guidelines listed in Appendix F: PSG Manual of Procedures. All technicians performing CHAT PSGs must be trained and certified on the CHAT montage and submit training verification to the Reading Center.









## Overview of Procedures for Baseline Visit

Participants will undergo:

- Brief orientation to testing facility and rest period
- Brief physical examination by the study physician or designee
- Resting morning blood pressures in triplicate
- Fasting venipuncture
- Anthropometry
- Breakfast and rest period
- Neurocognitive/behavioral testing and questionnaire completion
- Brief rest period
- Final eligibility confirmation
- Randomization in DMS
- Reaffirmation of informed consent and treatment arm assignment
- Review of all take-home materials, sleep and health education materials, use of Normal Saline Spray and Sleep diary

The Research Coordinator will also review the appointment schedule, provide the parent/legal guardian with a copy of the schedule and reaffirm the importance of maintaining the blind and following up on all study visits.

### Orientation

On arrival to the research facility, participant and parent/legal guardian (s) will be introduced to the research staff and provided with a brief tour of the facilities, using child-friendly approaches.

### Morning Resting Blood Pressure

Resting Blood Pressure will be performed on calibrated equipment by CHAT trained and certified site personnel only according to the guidelines listed in Appendix C: Resting Blood Pressure Manual of Procedures. Proper cuff size must be determined prior to obtaining the measurement. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from the standardized chart. After a 10 minute rest period, while the child is sitting, systolic and diastolic BP will be measured 3 times, at least 60 seconds apart, according to standardized guidelines. Proper cuff size must be determined prior to obtaining the measurement. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from a standard chart.

### Physical Exam

The Principal Investigator will review the participant's medical and sleep history and perform a brief standardized physical exam, including standardized assessment of tonsillar size, evaluation of the oro-pharynx and oro-cavity using Friedman and Mallampati position scales and identifying abnormalities on heart, lung, neurological and ears, nose and throat assessments.

### Fasting Venipuncture

Approximately 20 cc of blood will be obtained by venipuncture (and no more than 3 cc/kg body weight) after a minimum 10-hour fast and after preparing the skin with a local anesthetic. Within one hour of collection, specimens will be centrifuged and serum and plasma aliquoted, with removal and storage of the buffy coat if applicable. These specimens will be stored in a -80 C freezer, following instructions outlined in Appendix D: Laboratory Manual of Procedures. Assays will be stored locally and shipped on a monthly basis to LCBR. Analysis will include: insulin and glucose from plasma; and lipid profile and C-reactive protein from serum. Samples will also be stored for future testing and analysis of other inflammatory responses that may be associated with sleep apnea.

## DNA/Genetic Sampling

Participants and their parent/legal guardian (s) will be given the option to consent to genetic testing of stored blood samples. If parent/legal guardians (s) provide informed consent, the buffy coat from the blood samples will be stored to permit future DNA extraction. The purpose of DNA extraction will be to identify genetic variants associated with OSAS, OSAS-related health conditions (attention deficit disorder, diabetes, hypertension, hyperlipidemia, asthma/rhinitis, tonsillar hypertrophy), or associated with surgical response to OSAS treatment.

## Anthropometry

Children will be instructed to wear loose, lightweight clothing or change into a standard hospital gown. Weight (to 0.1 kg) will be measured on a calibrated digital electronic scale. Standing height (to 0.5 cm) will be measured with a stadiometer. Neck, waist and hip circumferences will be obtained to determine regional fat distribution. The neck waist and hip measurements will be repeated three times, and average values will be utilized, as defined in the Appendix B: Anthropometry Manual of Procedures.

Information will also be collected from the maternal parent (if applicable) as follows: birth weight of child and current height and weight of maternal parent and at the time of delivery.

## Neurocognitive and Behavioral Testing

### Overview

Each participant will undergo a series of cognitive and behavioral testing batteries (Table 1) conducted by a psychometrician from each site who is centrally trained and certified by the Neuropsychological (NP) Quality Control Center. Psychometricians will be supervised by a licensed psychologist and blinded to the treatment arm. Testing will be performed in a private, quiet room with adequate lighting and table space. Regularly scheduled breaks will be built into the testing sequence to avoid excess fatigue. Parent/legal guardian (s) will be asked to complete questionnaires in a separate room while their child is being tested as outlined in Appendix E: Neuropsychology (NP) Manual of Procedures.

### Test Administration

Two alternative testing batteries are offered to minimize the effects of test order, fatigue and circadian differences. Each participant will have the battery administered in the same order at baseline and Month 7. Psychometricians will alternately assign version set 1 or 2 as each subject comes in for testing. No other randomization process will be used. A tracking sheet entitled: [NPLOG] will be provided by the coordinator at study start-up and maintained by psychometrist. The coordinator will be notified of the version set assignment for notation in the participant's source file.

The order of each version and the expected amount of time to complete each section is outlined in the Table 1 and detailed in the NP Manual of Procedures. Each version set will begin with an "ice breaker" test, Beery-Buktenica Developmental test of Visual-Motor Integration (VMI) to acclimate the child to the testing environment.



**Table 1: NP Testing Version Set 1 and 2**

<b>Version 1</b>	<b>Section Times in minutes</b>	<b>Version 2</b>	<b>Section Times in minutes</b>
VMI	5	VMI	5
NEPSY-2 Word Generation	10	NEPSY Subtests	40
DAS-II	45	NEPSY-2 Word Generation	10
BREAK	10	CDI	5
WRAML-2 Verbal Learning	15	Peds QL	5
Purdue Pegboard	2	BREAK	10
NEPSY-2 Inhibition	8	DAS-II	45
WRAML-2 Delay	2	WRAML-2 Verbal Learning	15
NEPSY Subtests	40	Purdue Pegboard	2
CDI	5	NEPSY-2 Inhibition	8
PEDS QL	5	WRAML-2 Delay	2
Total Time to Complete	137 minutes (~2 hrs 15 min)*	Total Time to Complete	137 minutes (~ 2 hrs, 15 min)*

Children are expected to take up to approximately 3 hours to complete the assessment.  
Parent/legal guardian should complete questionnaires in 30-60 minutes.

Psychometricians note:

Baseline visit only: The component that determines final eligibility is the IQ summary score from the DAS-II. It is the psychometrician's responsibility to score DAS-II on the day of the baseline visit whenever possible so that eligibility can be finalized and confirmed by the unblinded research coordinator.

## **Role of Study Personnel during the Baseline Visit**

### **Principal Investigator (PI)**

The Principal Investigator will perform the physical exam and review the medical and sleep history. The exam will be performed according to the items listed on the Physical Exam 1 [PE1] CRF and will include the following:

- Temperature, Pulse, Respiration (can be taken by staff in the clinical research unit or clinic).
- Body System Exam
- Friedman Palate Position assessment
- Mallampati Position assessment
- Review of Medical History (including allergies) and current Medications

Additionally, during the baseline visit, the PI will be available to answer any remaining protocol/procedural questions, and assure that medical conditions associated with snoring are optimally treated (e.g., allergic rhinitis or asthma are under appropriate medical management) and that the appropriate follow up/referrals are made, if applicable. The Medical History [MEDHX] CRF may be utilized and reviewed with the child/parent at the time of the physical exam.

## Coordinator/Research Unit Staff or Research Assistants

Blinded or unblinded research personnel (coordinator/assistant) trained in CHAT study procedures may conduct this visit. To maintain consistency in data collection between visits every attempt should be made to have the same person conduct testing throughout the 7 month study period.

Blinded or unblinded research personnel (coordinator/assistant) trained in CHAT study procedures may conduct this visit as long as they are not serving a dual role (e.g. acting as PSG technician or administering NP testing). To maintain consistency in data collection between visits every attempt should be made to have the same person conduct testing throughout the 7 month study period.

The unblinded coordinator is essentially the “site project manager” and assures that all data are collected according to the guidelines listed in the Manuals of Procedures and that CHAT-certified personnel are carrying out the tasks, if applicable. For those sites utilizing a CRC, an in-service on the CHAT protocol and procedures must be conducted according to your institutional guidelines. CRC CHAT trained personnel must be listed on the Responsibility Log.

### Resting Blood Pressure

Resting blood pressure will be taken after the child has been oriented to the unit and has had a chance to rest for a period of at least 10 minutes. It is the coordinator’s responsibility to make sure that the resting blood pressure is obtained prior to the blood draw and NP testing. After a rest period, while the child is sitting, systolic and diastolic BP will be measured 3 times, at least 60 seconds apart, according to standardized guidelines listed in Appendix C: Resting Blood Pressure Guidelines. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from the chart listed in Appendix C: Resting Blood Pressure. The research coordinator is responsible for assuring that CRC staff is instructed on this procedure, if applicable.

### Anthropometry

Anthropometry is performed to assess the secondary aims of the study, including:

- The relationship of changes in growth to early surgery (EAT) vs. Watchful Waiting with Supportive Care (WWSC)
- Comparison of the effectiveness of adenotonsillectomy in children who are overweight vs. other children.

To accomplish this, all children will have the following measured at the baseline, 3 month and 7 month, examinations: height, weight, and waist, hip and neck circumferences. Height and weight measurements will be collected x 1 at each of these visits with the BMI calculated by the data management system (follow instructions on the ANTH case report form). Record the calculated BMI on the ANTH CRF as instructed.

- The neck, waist and hip measurements will be taken x 3 and recorded. An average of each of the variables will be calculated by the data management system and must be recorded in the shaded area on the ANTH CRF.
- Height and weight will be measured according to the guidelines listed in Appendix B: Anthropometry Manual of Procedures.
- Neck, Waist, and Hip Measurements (to 0.5 cm) will be made using a non-stretchable fiberglass tape (*Recommended: McCoy, Health Science Supply, <http://www.mccoymedical.com> Model No. 60, plastic case. MRP: \$5.50).*

All personnel performing Chat anthropometry measurements must be trained and certified according to the guidelines listed in the Appendix B. A record of certification must be provided to the DCC for regulatory purposes.

### **Blood Draw, Processing and Storage**

The coordinator/PI must assure that blood is collected, processed and stored according to the guidelines listed in the Appendix D: Laboratory Manual of Procedures. If clinical research unit or laboratory personnel are conducting this procedure, an in-service is required and must be documented. Personnel must also be identified on the Responsibility Log.

One roll of 25 “sets” of labels will be distributed to each site as needed with an instruction sheet. Each set includes labels for 25 participants at both time points when labs are required, Baseline and Month 7 (1 participant set = 52 labels). *Note:* Bar coded labels are not numbered according to CHAT PID. The LCBR uses a 4 digit system unrelated to CHAT PIDs. Assign sets of labels to CHAT participants as they enroll. Contact DCC for the next set of 25 labels, allowing up to 2 weeks for delivery.

Venous samples will be collected after an overnight fast of at least 10 hours using Child Life Principles (referenced in Appendix D). To aid in the child’s comfort, sites may use EMLA Cream or similar numbing agents, prior to initiation of the blood draw.

The blood should be drawn prior to breakfast, after the resting blood pressure measurements have been obtained and before the NP testing begins.

Tubes needed for blood draw:

- One 10 ml Red Top Tube (not serum separator or “tiger” top)
- One 10 ml EDTA or Lavender top tube

### **Parent/Child Questionnaires**

The site coordinator will assist the psychometrician in data collection and form completion during the baseline and month 7 visits. Questionnaires must be completed at the time of the visit, in the clinic, under supervision (e.g. assuring that CHAT-trained personnel are available if parent/child needs assistance) and under no circumstances, should questionnaires/forms be mailed or sent home with parent/child for completion. To assure consistency in data collection at the follow up clinical visits, the parent/legal guardian should accompany the child rather than another family member.

### **Psychometricians**

The cognitive and behavioral tests were chosen to emphasize measurements sensitive to sleepiness or intermittent hypoxemia, but also include tests of overall cognitive ability, memory, language abilities, psychomotor skills, behavior, and mood. Each test is standardized, has normative values across the study age range, and acceptable psychometric properties. All of the test measures have undergone extensive standardization and validation in children aged 5.0-9.99 years, with age-specific z-scores available. The comparability of data obtained across this age range is supported by evidence of similar factor loadings of intelligence subtests across the school-age range, as well as by evidence for good stability of test scores in assessments of cross-age test-retest reliabilities.

Two batteries (Version 1 and 2) which present the tests in an alternative order over the morning testing period will be offered. This will minimize effects of test order, fatigue, and circadian differences. For each child, the test battery will be administered in the same order at baseline and follow-up exams. Each version set will begin with an “ice breaker” test, Visual Motor Integration (VMI) to acclimate the child to the testing environment. The order of each version and the expected amount of time to complete each section is outlined in Appendix E: Neuropsychological (NP) Manual.

## Materials Distributed at the end of the Baseline Visit

After all testing is completed and the child/parent questionnaires have been completed and checked for completeness, the unblinded coordinator will meet with the family to distribute take-home materials and provide instructions on their use. *Note:* Distribution of materials may occur before or after randomization and is determined according to what works best for the staff at each site.

## Parent/Legal Guardian Diaries

To assess the possible influence of changes in sleep duration, sleep habits, and general activity over the course of the study, each parent/legal guardian will complete a sleep-activity log for 5 days recording their child's bed and wake time, major sleep awakenings, daily naps, caffeine use, and general activity levels. This log will also be used to capture over the counter and prescribed medication use, including use of the study nasal saline spray during the 5 days that the sleep activity is recorded. The 5 day Sleep Journal template (including cover sheet and directions) is listed in Appendix H: Supplemental Materials and should be copied and distributed to the parent for completion. A self-stamped return envelope should be provided for return of the diary at the end of the 5 day recording period.

The diary will be reviewed for completeness upon its return and each day will be entered into the DMS according to the instructions listed in Appendix J. The DMS contains a 1-page CRF [SLEEP] that must be entered for each day the diary was completed (up to 5 days).

## Educational Materials

Parent/Child education materials will be dispensed at the end of the baseline visit according to the table listed in the *Education Materials Binder (version set May 24 2007)* provided during training or sent electronically.

- Child: Garfield Fun Pad and My Pyramid Coloring Page
- Parent: TV Viewing, My Pyramid Up Close, My Pyramid Kids and Parents – Tips

## Normal Saline Solution

All participants will receive a generic brand of an over-the-counter saline nasal spray to use as needed for nasal dryness and crusting. Proper use of the spray will be reviewed with the parent/legal guardian and child. The bottle will be labeled with dose and frequency and recorded on the Saline Log [SALOG] with the lot number. For tracking purposes, parents will be instructed to return the bottle at the 7 month visit, whether or not it was used. Families will be queried throughout the trial on the use of the nasal spray.

The nasal spray is shipped from the Scientific Core at Case Western directly to the clinical site. The initial shipment will be supplied once IRB approval is obtained and training has been conducted.

## Visit Schedule and Contact Information

Prior to leaving the clinic, a copy of the visit schedule should be reviewed and provided to the family. To assist in retention, reaffirmation (verbal) of the informed consent and treatment arm assignment should be reviewed. Families will be instructed to contact the unblinded coordinator for all study-related questions/issues that arise during the course of the trial and the importance of maintaining the study blind will be reiterated.

## Randomization

### An Administrative Function

Randomization is an administrative function that should occur during the baseline visit while the parent/legal guardian and child are still in the clinic and once all eligibility criteria are known and entered into the DMS. In the rare case that it cannot occur on the same day as the baseline visit, (e.g. unblinded coordinator not available or not conducting visit, for example), then randomization must take place within 48 hours of the baseline visit. *Note:* A phone call to the parent/legal guardian assuring that changes to the child's health status (AEs or changes in medications) has not occurred in the interim will be required if randomization is not conducted on the day of the baseline visit. *Refer to the Data Management System's User's Guide for details. [RAND] CRF must be completed and maintained in a secure location.*

### Post Randomization Scheduling of Key Visits

Once families are informed of the treatment arm assignment and the study procedures, consent and follow up visits has been reaffirmed, the unblinded research coordinator is responsible for assuring that the following appointments are scheduled and diaries and teacher questionnaires are distributed:

#### EAT Arm Only

AT surgery must occur within four (4) weeks of randomization (refer to Appendix G: Surgical Manual of Procedures for details). The unblinded coordinator must work closely with the family, the lead otolaryngologist and ENT clinical staff to arrange AT within the study time frame.

#### WWSC Arm Only

Children randomized to the Watchful Waiting Supportive Care arm are reevaluated by the otolaryngologist within 1- 4 weeks of the month 7 visit. To avoid delays, this visit should be scheduled with ENT as soon as the randomization assignment is known. The unblinded coordinator must schedule the ENT re-evaluation visit within 1-4 weeks of the date listed on the participant's visit schedule (generated by the DMS).

#### 6 Month PSG

Arrangements should be made to schedule the 6 month follow up PSG as soon as possible after randomization has occurred. Blinded site personnel may assist the coordinator with this task and inform h/her of the date.

### Handling Teacher Ratings/Questionnaires/Contact

If the child is in school, the teacher questionnaires will be sent out to each child's *current* teacher (or prior year if during summer months) to complete and return at the baseline and Month 7 visits. These forms are not accessible in the DMS and should be available at each site for distribution (Brief and Conners' Teacher from the psychometrician/neuropsychologist). Mailings should occur between 2-4 weeks prior to the baseline and 7 month visit.

If a teacher questionnaire has not been returned by 1 week after a child's visit the coordinator will call the teacher to inquire if he or she has any questions about the process or needs another packet. As indicated in the cover letter, teacher return of questionnaires will be voluntary and will not affect a subject's participation in the study. To minimize missing data, teachers will receive a \$10 honorarium for returning questionnaires.

## Distribution of Parent/Legal Guardian Diaries

To assess the possible influence of changes in sleep duration, sleep habits, and general activity over the course of the study, each parent/legal guardian will complete a sleep-activity log for 5 days recording their child's bed and wake time, major sleep awakenings, daily naps, caffeine use, and general activity levels. This journal template is listed in Appendix H: Supplemental Materials. It will also be used to capture over the counter and prescribed medication use, including use of the study nasal saline spray.

Parent/guardian(s) will be instructed on the proper use of the diary. Recording of sleep habits and general activity will start at baseline (sit with parent and record the child's sleep pattern from the night before and instruct parent to complete the next 4 nights and return diary in self-addressed prepaid envelope.) The sleep diary should be distributed again at the 6 month PSG for completion by the parent for a period of 5 days (do not include the night of the PSG) and returned at the 7 month visit.

## Study Visits

(Randomization) through Month 7 – 8

### Table of Visits Month 1 through Month 7- 8

Time	Visit Number/Code	ALL PARTICIPANTS (BOTH ARMS)	EAT ONLY	WWSC ONLY
Month 1	5 (T1)		AT Surgery	
Month 2	6 (V1)	Phone Contact		
Month 3	7 (V2)	Clinical Visit (No NP testing at this visit)		
Month 5	8 (V3)	Phone Contact		
Month 6	9 (V4)	Overnight PSG		
Month 7	10 (V5)	Clinical Visit (NP testing)		
Month 7-8	11 (T2)			ENT Reevaluation

## Visit Preparation

### Overview

- Appointment scheduling: An appointment will be made for each participant according to the randomization assignment and should occur by the "Close Window" date listed on the participant's schedule (generated by the DMS). The visit window is 14 days; + or - 7 days from the Target Date listed on the schedule. All visits should be completed by the "Close Window" date or they will be considered missed visits. A protocol deviation / violation form must be completed for visits that are missed completely or occur out of the window. Refer to Appendix H for the Protocol Deviation form.

- Visit Packets: Visits packets are numbered 1 through 11 and can be printed from the DMS at anytime.
- Data Processing Cover Sheet [DPCS]: A list of all forms required for a particular visit. Included with each visit packet.
- Concomitant medications: The unblinded coordinator must track ongoing and new medications on the CMED Log at each visit.
- Adverse Events: The unblinded coordinator must track adverse events including worsening of preexisting conditions (such as OSAS) and serious events on the AE Log at each visit.
- Reminder Call to Parent/Child: As a *retention mechanism*, a phone call reminding the parent/legal guardian and child of their upcoming clinical visit is recommended. Participant Treatment/Follow-Up Contact Visits
- Payments for travel costs as listed in the protocol and in accordance with local IRB.
- Consider additional incentives such as water bottles, coloring books, etc.

### **EAT Arm – Surgery – Month 1**

The unblinded coordinator must coordinate scheduling of surgery within 4 weeks of the date of Randomization and no later than the close window date listed on the participant's Visit Schedule (indicated as Visit 5: Surgery). The window reflects + or - 7 days of the target date. Surgery can be scheduled before the open window date listed on the schedule but no later than the close window date. The ENT surgeon must be provided with the Intraoperative data collection form [OPER] for completion at the time of surgery. Refer to Appendix G: Surgical Quality Control Core Manual of Procedures for coordination of intra and post operative data collection and forms. Pre-operative blood work should be completed according to the instructions provided to the family when surgery is scheduled.

#### ***Special Considerations for EAT ARM***

##### **Intraoperative Photos**

All participants having surgery in the EAT ARM must be listed on the Surgical Log [SURLOG], an administrative form that is available through the DMS, in order to track every 10<sup>th</sup> surgery for the purpose of coordinating intraoperative photos with ENT. The photos will be sent to Susan Garetz, MD, Director of the Surgical Core via an encrypted zip file to the following email address only: [sq48104@comcast.net](mailto:sq48104@comcast.net)

*Refer to Appendix G for complete details.*

##### **PSG Results**

The unblinded coordinator must notify the surgeon if the research PSG is reported by the Reading Center as:

- AHI >20, OAI >15, or marked desaturation is seen (percentage oxygen desaturation of <92% for >2% of sleep time)

The Reading Center is blinded to the treatment arm assignment and will initiate an Urgent Alert Notification for *all participants who meet the above criteria, regardless of arm*. The unblinded coordinator will notify the ENT surgeon performing the surgery since these levels may influence perioperative care.

## WWSC Arm Only - Reevaluation Visit – Month 8

Participants randomized to the Watchful Waiting with Supportive Care Arm will be re-evaluated by an otolaryngologist to determine if surgery is required. It is the unblinded coordinator's responsibility to assure scheduling of this visit.

This appointment should be scheduled with ENT at the time of randomization to occur within 1 to 4 weeks after the 7-month primary end point visit. Symptoms and PSG findings (baseline only) will be reviewed by the ENT and a decision whether to proceed with AT as part of routine clinical care will be made. The surgeon must complete the Re-evaluation Case Report Form.

## Follow up Phone Contacts

Families in both arms will be contacted by phone for safety and adverse event monitoring and to reinforce general study participation at Month 2, 5 (refer to Tables 1 and 2 on the previous page). The follow up phone contact visits for all participants occur, in most cases, at 2 month intervals from the study start date (time of randomization) with clinical visits in-between.

## Data Collected at Phone Visits (Both Arms)

Data will be collected using the form [PHONE] at Month 2, 5, for all participants enrolled in the study regardless of arm. The unblinded coordinator will assess for and record any new adverse events since the last contact by asking: "*Since your child's last visit, has he/she had any new symptoms, injuries, illness, or problems?*" AND "*Since your child's last visit, has he/she had any worsening of pre-existing conditions?*" All changes in medications and health status will be documented on the [PHONE] form and recorded on the [CMED] and [AE] logs.

## EAT Arm Only – Follow Up Phone Contact Post Surgery

In addition to the above information, participants in the EAT arm will also be queried for post surgical AEs utilizing the forms:

- Post-Operative [POST1] (Month 2 via phone contact)
- Post-Operative [POST2] (Month 5 via phone contact)

Investigation of reported information may require a review of the ENT clinical chart. *Refer to Appendix G: Surgical Quality Control Core Manual of Procedures for details.*

## Clinical Visits Both Arms

Each participant returns to the clinic for symptom assessment at Month 3 and 7. All participants receive a follow up PSG at Month 6.

### Month 3

A brief clinical visit will be conducted to obtain anthropometry measurements, resting blood pressure and general symptom assessment including new signs or symptoms requiring further evaluation. The unblinded coordinator will:

- Assess if changes in health status have occurred since last contact/visit
- Inquire about medication changes
- Reinforce the treatment arm assignment and study blind



- Review visit schedule
- Provide take home educational materials: PJ Bear Time to Sleep Comic Book (may be copied from Education Materials Binder provided during central training).

### **Month 6 PSG**

One to two days prior to the scheduled follow up research PSG, families will be contacted to remind them of the visit and to ensure that intervening medical illnesses have not occurred, requiring the visit to be rescheduled. These include any of the following within the previous 7 days:

- febrile illness
- upper respiratory illness resulting in increased coughing
- nasal problems acutely interfering with sleep

As with the screening PSG, participants will be instructed to report to the sleep laboratory at least 1 hour before their usual bedtime and remain at the sleep laboratory in a quiet dark room until the study ends the following morning. Lights off will be at approximately 2100 and lights on no earlier than 0600. Children are encouraged to maintain their usual daily routine. Neither sedation nor sleep deprivation is used to induce sleep. Children will be accompanied by at least one guardian during the night.

### **Month 7 Clinical Visit (End Point)**

The major study endpoints will be measured at 7 months following baseline assessments. Each participant will undergo the same procedures described for the Baseline Visit.

- Brief physical examination by the study physician or designee
- Resting morning blood pressures in triplicate
- Fasting venipuncture
- Anthropometry
- Breakfast and rest period
- Neurocognitive/behavioral testing and questionnaire completion
- Brief rest period
- Review of AMBP Placement

Techniques will be identical to the Morning Baseline Visit and the child/parent/legal guardian should be reminded not to reveal the treatment arm assignment.

### **Missed Study Contacts (Visits)**

#### **Rescheduling of Testing and Tips for Retention**

If a participant does not keep a scheduled appointment, with a within the 14 day window of its due date, the missed visit including phone follow up must be attempted and/or rescheduled as soon as possible to complete the testing required for that visit and to query the parent about the child's health status.

To minimize the occurrence of missed appointments, the parent/legal guardian (s) will be provided with the following reminders when appropriate:

- Written schedule of visits during the baseline exam with reminder at each contact
- Printed card with date of next visit or contact (when appropriate)
- Advance notification of next visit (at least one week prior)

- Phone call reminder within 1 to 2 days prior to the scheduled visit
- Letter via postal mail if other methods of communication fail

If a follow-up contact cannot be completed within the time window allowed, the contact should be scheduled and completed before the window date of the next study contact. If the contact cannot be completed before the window date of the next contact, the contact must be considered missed, and the visit should be marked as missed in the database.

When a participant misses a follow-up contact, the unblinded coordinator should stress to the family the importance of collecting follow-up data. When a participant misses multiple follow-up contacts, the PI may consider withdrawing the participant from the study.

A Protocol Deviation and Violation Form must be completed for each participant who has a visit outside of the window and/or misses an entire visit. A copy should be sent to the DCC. This form does not get entered into the DMS and is for administrative purposes only

## **Adverse Events and Pre-Existing Conditions**

### **Overview and Definitions**

The following section *defines* pre-existing conditions and adverse events. A thorough medical history must be obtained from the child's parent/legal guardian (s) to provide ongoing monitoring of any changes in pre-existing symptoms (e.g. OSAS) and to allow comparison of new adverse event information as it may relate to a condition that existed prior to participation in the study.

### **Adverse Event (AE)**

An adverse event is any unfavorable or unintended sign, symptom or disease occurring in a clinical trial participant at any stage of the study.

Adverse events may include the following:

- All suspected adverse medication (or device) reactions, drug interaction,
- Worsening of a pre-existing condition, or apparent unrelated illness.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.
- Any event that could be characterized by the definitions above is an AE, whether or not considered related to the study.

### **Adverse Event Reporting Period**

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study follow-up. For this study, the study treatment follow-up is defined as the last scheduled visit. *Note:* SAEs that are ongoing at the end of the study period must be followed to determine the final outcome. Any SAE that occurs after the study and considered to be possibly related to the study treatment or participation should be recorded and reported to the DCC.

### **Baseline-Emergent Adverse Event**

Defined as any event that occurs or worsens during the staged screening process (after informed consent) including the randomization visit.

## Expected (Anticipated) Adverse Events

Adverse events that are expected and are identified in the protocol and for the purpose of this study have been identified as:

- Foreseeable (expected) mild adverse events that may not warrant reporting
- Foreseeable (expected) adverse events that exceed threshold definitions and warrant reporting

### Foreseeable (expected) events that may not qualify for AE Reporting

The Office of Human Research Protection distinguishes between risks and discomforts that are related to research compared to clinical intervention and have defined new reporting guidelines as of January 17, 2007 (refer to the protocol for details). Since the surgical procedure (AT) is being performed as part of routine clinical care (e.g., it is not paid for as a study procedure and is performed as part of routine clinical care), all foreseeable mild AEs that are expected to occur at high frequencies as part of routine clinical care including those associated with surgery (AT) that do not exceed threshold definitions as defined in the tables below will not be considered adverse events and will not warrant reporting.

### Foreseeable (expected) events that exceed threshold definitions and warrant reporting

Foreseeable events that warrant reporting have been identified by each specialty group involved with the study. Adverse Events that warrant reporting are those that exceed the threshold definitions listed in the tables below.

## Laboratory Values

A laboratory abnormality should be documented as an adverse event if:

- The abnormality suggests a disease and/or organ toxicity, *OR*
- The abnormality is of a degree that requires active management; (e.g. specific treatment, more frequent follow-up assessments, further diagnostic investigation, etc.)

*AND*

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.

## Laboratory Alerts

Laboratory Alerts are defined below. The LCBR will report results directly to the site PI for follow up. *The tests will be repeated locally to confirm.*

- Fasting blood sugar > 126 mg/dl
- Lipid Panel:
  - Total cholesterol > 200mg/dl
  - LDL cholesterol > 130 mg/dl
  - HDL cholesterol < 35 mg/dl
  - Triglyceride > 150 mg/dl

*Note:* Participants and their parent/legal guardian (s) will not be informed of any of the results collected and processed in the future for research purposes. These are research data only and not meant for the purpose of diagnostic evaluation. The results will not become part of the participant's medical record.

## Non-serious Adverse Event

A Non-serious AE is any adverse event that does not meet the criteria for “serious” according to grading scale and/or as identified in the AE Tables at the end of this section.

## Potential Treatment Failures

Potential treatment failures are signs and/or symptoms that could potentially indicate treatment failure regardless of the arm assignment and are reported to the Independent Medical Monitor for final determination. *Refer to item 8 below for treatment failure definitions.*

## Pre-Existing Condition

Preexisting conditions are chronic or acute signs, symptoms, illnesses, or health issues that the participant has at the time of consent and screening. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings or abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

## Serious Adverse Event (SAE)

Any event that is life threatening or fatal; results in significant or persistent disability; requires hospitalization or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. The appropriate case report form must be completed for all events in this category according to the guidelines listed in the Manual of Procedures.

## Treatment Failure

Treatment Failures are defined as conditions that may require additional/alternative therapies that may or may not be exclusionary criteria and are designed to minimize the potential risks to participant’s safety:

- 1) Child’s physician has identified a change in signs or symptoms that in his/her opinion warrant alternative treatment for OSA. Examples of such changes in clinical status include:
  - new academic or behavioral problems resulting in a recommendation for grade retention
  - special education
  - counseling or placement on medications for behavior, or emotional problems
  - new medical problems including 3-5 below
- 2) Recurrent bacterial tonsillitis defined as 3 or more episodes of streptococcal culture positive infection occurring over a 3 month time interval. Children who have medical chart documentation of 3 culture positive infections will be asked to undergo a repeat throat culture after completion of the third course of antibiotics to exclude a chronic carrier state. If this test is not ordered for routine clinical purposes, it will be arranged by the RC and paid for by the study.
- 3) New clinical diagnosis of cor pulmonale
- 4) Development of “failure to thrive” defined by weight loss during the course of study follow-up characterized by:
  - i. Weight falling below the 3<sup>rd</sup> percentile for age and gender **OR**
  - ii. Weight falling by two or more major isobars on the weight for age CDC percentile charts (<http://www.cdc.gov/growthcharts> **AND**

- iii. The weight loss is not better explained by either an intentional weight loss (as part of healthy life style changes) or a transient loss related to an intercurrent acute illness such as viral gastroenteritis.

**Note:** this definition excludes children whose baseline BMI is  $\geq 85\%$  for age and gender.

- 5) New onset of Stage 2 hypertension that is not better explained by another medical condition (for example, nephrotic syndrome).
- 6) New-onset hypersomnolence defined as reports of falling asleep on average > 3 times per week at school (not planned naps) despite spending adequate time in bed overnight (at least 10 hrs per night) that is not better explained by other factors unrelated to OSA (for example, intercurrent use of a new medication such as a sedating antihistamine). *These criteria only apply to children attending school.*

### Treatment Failure Defined by Arm

In addition to the descriptions listed above, the following arm specific treatments are classified as Treatment Failures:

**Note:** If alternative treatments are required, regardless of treatment arm assignment, the participant will remain in the study and will be followed until all visits and procedures have been completed.

### Early Adenotonsillectomy (EAT)

- Initiation of Continuous Positive Airway Pressure (CPAP) after AT surgery.
- Revision AT surgery, as clinical indicated.

### Watchful Waiting Supportive Care (WWSC)

- Cross over to AT surgery for any of the reasons listed above.
- Initiation of Continuous Positive Airway Pressure (CPAP).

Parent/legal guardian(s) who decide that they no longer want to wait until the 7 month primary end point visit for their child to be re-evaluated for AT surgery, but whose children do not meet any of the criteria for treatment failures, *are not considered treatment failures*. These children will be reevaluated by the ENT physician who initially evaluated them, unless they prefer to seek other medical consultation.

### Unanticipated Problem Involving Risks to Subjects or Others

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

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to a subject's participation in the research
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

## Unexpected Adverse Events

Adverse events that are not expected and not identified in the protocol or consent form according to the tables listed at the end of this section. Adverse Events in this category will be reported.

## Other Definitions

### Intervening Medical Illness

Scheduling/re-scheduling study-related visits if the child is ill:

30 days from the time of an acute exacerbation of illness requiring hospitalization or systemic steroids or 14 days from the time of a fever or an illness of sufficient severity that it required the child to miss 2 or more days of school/pre-school or be confined to bed for 2 or more days.

### Urgent Medical Referral

Conditions that will generate an Urgent Medical Referral Alert (UMRA) are those laboratory, physiological, or behavioral findings that are believed to represent conditions that may require additional evaluation by the participant's health care providers in a timely manner. Thus, if the following conditions are identified during the course of the study, their occurrence will generate an Urgent Medical Referral by the Site PI who will communicate with the participant's guardian, and with permission, contact the child's health care provider. Some of these conditions (abnormalities of blood pressure) will be noted as usually needing confirmation with repeat testing before clinical diagnosis can be made.

Urgent Medical Referral Criteria include:

- Stage 2 Hypertension (> 99% for age and gender)
- Overnight sleep time desaturation of < 90% for > 2% of sleep time, OAI >20, AHI >30,
- CDI score of > 70
- DAS-II- score of ≤ 55 on summary IQ.

It should be noted that if any of these conditions occur after enrollment (i.e., not during a screening visit that disqualifies the child from enrolling in the study), these conditions, as well as others identified in the AE Tables at the end of this section, will also be reported as Adverse Events.

An *Urgent Medical Referral Alert* should be completed within 24 hours of first knowledge of the event.

## Ongoing Participant Assessment for Adverse Events

### Overview

The Investigators (ENT, NP, site PI, Reading Center PI, if applicable) and unblinded study coordinator should assess each participant for adverse events (AE) throughout study participation. This includes conducting a thorough investigation on any suspected AE that may come from a variety of sources:

- Spontaneous reports by participant
- Observations by key study personnel
- Reports to study staff by the participant's family or medical care providers

- Possible AE documented in medical records, progress notes, etc.
- Death of participant
- In addition to receiving reports of potential AEs, the Investigator and Study Coordinator should develop and implement a plan to consistently and routinely monitor for AEs through proactive measures such as:
  - Interview participants/parent/legal guardian (s)
  - Review lab reports
  - Review participant's medical records for additional information
  - Review participant's diaries
  - Communicate with participant's medical providers

In order to maintain the integrity of the study blind, the unblinded research coordinator will instruct parent/legal guardian(s) to contact him/her directly during the course of the study when any new, questionable, untoward, or worsening preexisting condition occurs. The unblinded research coordinator will facilitate follow-up, if applicable.

### **Baseline PSG Results indicating Severity of OSA**

Severity of the child's Obstructive Sleep Apnea will be determined by PSG scoring and review at the reading center. Any PSG study meeting Urgent Medical Referral criteria (i.e., upper limits for study inclusion based on OAI, AHI and desaturation) will be identified with 48 hours of its receipt at the PRC, will be reviewed by the PRC Director, with an Urgent Referral Alert Notification electronically transmitted to the study coordinator and site PI, who will facilitate appropriate clinical management. Children so identified on baseline studies will not be eligible for randomization, so providing such data to the PI will not contaminate outcomes. Data from follow-up PSGs will be available at a time when all follow up data have been collected to minimize influencing study outcomes, an approach that is standard for research data. An exception is for any information identified that may pose acute health risks or would influence immediate treatment, in which case such data will be shared earlier.

Surgeons will be informed of the baseline research PSG for children randomized to EAT if the AHI >20, OAI >15, or if marked desaturation is seen (percentage oxygen desaturation of <92% for >2% of sleep time), since these levels may influence perioperative care.

All Urgent Referral Alerts will be logged into a PSG Alert Log at the Reading Center indicating the date reviewed and date site PI and Surgeons were notified. The site will receive the Sleep Report and quality grades (QS form). All remaining studies are scored based on date received. Bi-monthly review of scored studies by site by scorer is done to maintain equal distribution of studies from all sites among the scorers.

### **Eliciting and Monitoring Pre-Existing Conditions and Adverse Events**

Consistent with clinical research adverse event reporting guidelines, the reporting of adverse events will be accomplished by collecting information on adverse experiences during the screening process and at all treatment and follow-up visits. The coordinator and/or the PI should interview each potential child/parent/legal guardian in a manner that is friendly but solicitous of a response in order to ascertain as many pre-existing conditions as possible. All adverse events (non-serious and serious, baseline and treatment-emergent) must be recorded on the Adverse Event Report Form. Refer to DMS User's guide for details.

## Pre-existing Conditions

Information will be systematically collected by the RC and/or PI during the screening and baseline visits. Pre-existing condition information will be derived from child/parent/legal guardian interview and medical condition as assessed at during the screening/baseline phase. A record of all pre-existing conditions will be collected on the Medical History [MEDHX] CRF, maintained in the participants source file and entered into the DMS. To track worsening of pre-existing conditions over the course of the trial, the parent/legal guardian will be queried at all visits including phone contacts for worsening symptoms.

## Adverse Events Guidelines

### Coding

To aid in defining symptoms and events in a standardized fashion an online tool will be utilized as described in detail in the Data Management System User's Guide section.

#### *Common Terminology Criteria for Adverse Events*

The CTCAE Dictionary enables clinical trials researchers to access the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria at point of care. The application provides quick access to the CTCAE Dictionary and allows search of adverse events by category, index, or keyword.

Personnel who have been trained and certified on the use of the CHAT DMS were also given an overview of the use of the CTCAE Directory. *Refer to the Data Management System User Guide for details.*

**Pediatric Considerations:** The CTCAE online tool is available to assist with naming and identifying the Adverse Event and its [preliminary] severity grade. The guidelines are general in nature and although written for both children and adults, variations may exist for pediatric patients that are not listed (laboratory ranges, for example). The guide is intended to use in conjunction with the AE Tables listed below (Item 3).

## Recording and Reporting Non-Serious Adverse Events

At each contact with the subject, the unblinded coordinator must question the family about any new sign or symptom and/or worsening pre-existing condition and changes in medications. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate AE module of the case report form (CRF).

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The following data will be recorded

- Any event reported by the participant or parent/legal guardian (s), during the course of the trial other than those listed as mild and expected in high frequency as listed in the AE Table at the end of this section.

Signs and Symptoms will be graded initially by the unblinded coordinator with final review and sign off by the PI after the blinded phase of the study has passed for that individual *or* as required based on the severity of the adverse event.

## Follow Up of Adverse Events

The unblinded coordinator and/or clinical investigator will follow every AE to a satisfactory outcome or stabilization of the event, even when it requires a time period beyond the scope of



the study. The clinical investigator will record each AE outcome on the case report form according to the instructions outlined in DMS User's Guide after the blinded phase of the trial has ended for a particular child.

### **Post-study Adverse Event Follow Up**

All unresolved adverse events should be followed until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant and parent/legal guardian (s) to report any subsequent event(s) that they believe may be related to participation in this study.

If there is an SAE, which is thought by the Medical Monitor to be possibly or probably related to the coded intervention, the clinical site, when necessary for the safety of the participant, will unmask the treatment arm assignment. The medical monitor will determine if unblinding is necessary after consultation with the PI and ENT.

## **Management of Associated Non-Serious Adverse Events**

### **Discontinuation of Treatment**

The administration of the intervention may be discontinued at the subject's request or by the investigator, based on clinical judgment. If the subject is withdrawn from the study and participation terminated, the Study Stop (SSTOP) and Treatment Stop (TSTOP) CRFs must be completed documenting the date study participation ended and identifying the reason. Parent/legal guardian (s) of participants who are discontinued will be instructed to report any AE experienced after treatment without delay.

### **Other Study Medical Monitoring and Reporting**

#### **Surgical Monitoring**

Complications resulting from surgery will be documented at each site with use of an intra-operative data sheet and by reports obtained from the family during routine interim follow-up, supplemented by medical records, as appropriate. Major unanticipated adverse events and unanticipated problems that fit the reporting criteria are required to be reported to your institutional IRBs. The DCC will report unanticipated complications from surgery to the SQCC, the Steering Committee, IMM, DSMB and NHLBI. Periodically, these results will be tabulated and any significant deviations from reported national rates will be investigated. If any surgical complication is noted that exceeds expectation of usual care, or any site experiences excessive problems (as defined by the SQCC or the DSMB). Dr Garetz, Director of SQCC, will initiate an investigation. Actions may include ongoing monitoring, retraining, excluding the participation of specific surgeons, or excluding specific sites.

### **Serious Adverse Events**

The unblinded coordinator will follow the general guidelines for query of a potential SAE as listed in item 2 above. DCC Project Management must be notified within 24 hours of first knowledge of the event via phone, email or fax at:

Mrs. Kim Lacy, RN, BSN  
Project Manager  
University of Pennsylvania  
Clinical Research Computing Unit (CRCU)  
Center for Clinical Epidemiology and Biostatistics (CCEB)  
University of Pennsylvania School of Medicine  
3535 Market Street, Suite 560  
Philadelphia, PA 19104-3309  
(T) 215.573.0172  
(F) 215.573.6262  
Email: lacyk@mail.med.upenn.edu

If the Project Manager is not available, please contact Rosemary Madigan at rmadigan@mail.med.upenn.edu, phone 215.573.6314 or Denise Cifelli at cifelli@mail.med.upenn.edu phone: 215.573.4534.

### **Serious Adverse Event/Potential Treatment Failure Report Form (SAE/PTF)**

Upon notification from the site, the project manager at the DCC will send the unblinded coordinator the site-specific Serious Adverse Event/Potential Treatment Failure Report Form to complete electronically. For administrative purposes, this form is only sent to the sites as SAE and PTFs are reported and is not available for printing from the DMS. The information on the form does not get entered into the DMS and is a mechanism for reporting purposes only. Project Management will provide an initial introduction/overview of the form to the unblinded research coordinator at each site and will also be available for assistance as necessary.

The SAE/PTF report must be completed within 48 hours of receipt and will be submitted to the DCC and Medical Monitor simultaneously via email as a password protected attachment. Instructions for completing this information will be listed on the form. Diagnostic information that will assist in the understanding of the event may be requested and follow up reports may be required.

The Medical Monitor will respond within 48 hours with his recommendations.

All Significant new information on ongoing serious adverse events should be provided promptly to the DCC.

Potential Treatment Failures (PTFs) may not be due to a Serious Adverse Event. PTF will be deliberated by the Medical Monitor unless there is a prolonged period when he anticipates being completely unavailable and in that case, the DCC will determine if a back up monitor is required on a case-by-case basis.

### **Recording and Entering SAEs into the DMS**

In addition to above, all SAEs are recorded on the Adverse Event (AE) CRF and entered into the DMS. *Refer to Data Management System User Guidelines for details.*

The site must promptly report all SAEs to their IRB via written, dated notification in accordance with the IRB's reporting requirements. Copies of all such correspondence must be maintained in the clinical site's regulatory binder.

SAEs that are ongoing at the end of the study period must be followed to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

## Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization, should be documented and reported as a **serious adverse event** (SAE) unless it is AT surgery occurring as treatment in CHAT. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

*A note about Emergency Room Visits:* In some case, families may utilize a local emergency room as their primary care-giver. If the family reports an ER visit during the course of the trial, interrogation into the event may be necessary to determine the “type” of visit that occurred. ER visits that are not true emergencies are not included considered hospitalizations. However, the reason for the visit (signs and symptoms and/or diagnosis if available) and treatment received is recorded on the Adverse Event and Concomitant Medication CRFs.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event if it occurred for a diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

### Unblinding Due to an SAE

If there is an SAE which is thought by the Independent Medical Monitor to be possibly or probably related to the coded intervention, the clinical site, when necessary for the safety of the participant, will unmask the treatment arm assignment. The IMM will determine if unblinding is necessary after consultation with the PI and ENT (when applicable). An explanation of the need for unblinding the treatment arm assignment must be provided to the DCC, who will disseminate the information to the various regulatory groups (DSMB, NHBLI) and external site PIs.

*Note:* Unblinding of the treatment arm assignment is anticipated to be an uncommon occurrence and is anticipated to be an uncommon occurrence and is highly discouraged.

### External Reporting of SAE/PTF

The DCC is responsible for reporting SAE/PTF to the monitoring bodies. Upon notification from the clinical site and verification from the medical monitor, any serious adverse event that might reasonably be due to the study intervention will be reported to the Executive and Steering Committees as required including, but not limited to, the University of Pennsylvania’s Office of Human Research, the DSMB, and the NHLBI within 7 days of its occurrence. DCC will also provide follow up reports when indicated.

AE/SAE Reporting Schema is listed on the next page.

**SAE and PTF Reporting  
Schema**

## Medical Monitoring

### Safety Monitoring

Since the PI at each site is blinded to the treatment arm assignment, the unblinded research coordinator, ENT surgeon (if applicable) and NP will have the primary responsibility of overseeing adverse events, ascertain their *preliminary* relationship to study, and coordinate follow up when applicable. This will include careful assessment and appropriate reporting of adverse events, potential treatment failures as defined in the protocol and

Safety monitoring will also include oversight by the Data Coordinating Center who is responsible for generating reports through regular assessment of the number and type of advents.

### Exceptions to unblinding related to participant safety

The PI must be notified *when a SAEs is reported that poses imminent risk to the participant and when* direct involvement by the PI with the child/parent/legal guardian is required to assist in prompt clinical management, referral and follow up.

### Independent Medical Monitor

A pediatrician unassociated with the clinical sites and Scientific Core will serve as an Independent Medical Monitor (IMM).

#### Independent Medical Monitor (IMM)

Timothy F. Hoban, MD  
University of Michigan  
Pediatric Neurology and Sleep Medicine

#### Alternate Medical Monitor (AMM)

Ron Chervin, MD, MS  
University of Michigan  
Michael S. Aldrich Sleep Disorders

The IMM will be notified by the unblinded coordinator at each site when a Serious Adverse Event (SAE) and/or Potential Treatment Failure (PTF) occur. The form utilized to report this event is only available by contacting the DCC. The SAE/PTF administrative report form the IMM will be informed of the treatment arm assignment in order to make an informed decision about the safety of a particular participant when a health care issue arises that warrants immediate attention. The IMM will respond within 48 hours of receipt of the report and may either request additional information or provide recommendations.

If a medical or psychological adverse event occurs that requires immediate intervention, it will be evaluated on an individual basis and study termination or recommendation regarding immediate AT surgery will be made.

The IMM will also evaluate both trends in AEs and Treatment Failures across the study and within each arm, as well as to confirm or refute the occurrence of specific treatment failures.

## Other Study Medical Monitoring and Reporting

### Surgical Monitoring

Complications resulting from surgery will be documented at each site with use of an intra-operative data sheet and by reports obtained from the family during routine interim follow-up, supplemented by medical records, as appropriate. Major unanticipated adverse events and

unanticipated problems that fit the reporting criteria are required to be reported to your institutional IRBs. The DCC will report unanticipated complications from surgery to the SQCC, the Steering Committee, IMM, DSMB and NHLBI. Periodically, these results will be tabulated and any significant deviations from reported national rates will be investigated. If any surgical complication is noted that exceeds expectation of usual care, or any site experiences excessive problems (as defined by the SQCC or the DSMB). Dr Garetz, Director of SQCC, will initiate an investigation. Actions may include ongoing monitoring, retraining, excluding the participation of specific surgeons, or excluding specific sites. *Refer to Appendix G: Surgical Manual of Procedures for details.*

## **Neuropsychological Monitoring**

- The NP QA activities will be coordinated through the Neuropsychology Section at the University of Michigan, under the direction of Dr. Giordani.

### **Year 1**

- NP QA Coordinating Site will compare the source documents and CRFs for the first 10 patients assessed at each site
- Photocopies of source documents and CRFs will be provided by each CS.
- CRF evaluations will include checks for accuracy, legibility, and proper coding procedures
- Any discrepancies that are found will be resolved within 7 days with the originating site and corrected CRFs will be sent to the DCC by the testing site

*Refer to Appendix E: Neuropsychological Manual of Procedures for details and post year 1 monitoring.*

## Case Report Forms (CRFs)

Sample forms and instructions for completion are located in Appendix I

### Acquisition of Case Report Forms

- Case Report Forms (CRFs) are available to the Clinical Centers as Adobe PDF files, and are accessible from the Main Menu of the Data Management System (DMS).
- The Unblinded Research Coordinator (RC) will be responsible for maintaining sufficient CRF packets for patients. The Data Coordination Center (DCC) is not responsible for creating multiple copies of CRFs. The DCC will notify the Clinical Centers (CCs) of revisions to CRFs, introductions of a new CRFs, and subsequent updates to the DMS. The DCC will instruct the RCs how to incorporate CRF changes into the study and how updates will impact the DMS.
- Administrative forms will be supplied to provide additional information and supporting documentation of the day-to-day study functions. However, these forms are not entered into the database.

### Submission of Case Report Forms

- The DCC may request copied CRF submissions on a random sample of participants to perform database audits.
- For those CRFs sent for audit purposes, CCs will follow established guidelines to maintain patient confidentiality, which must be strictly followed. Including, but not limited to, blackening out any confidential participant information with a thick black marker on copied CRFs prior to submission to the DCC.
- The CCs will maintain a locked filing system for all study-related materials and completed CRFs. Confidential data (PTCON, RAND, and Consent Forms) must be kept in a locked filing cabinet, separate from the rest of the study data, and accessible only by the unblinded RC.
- CCs must remove any sensitive participant information from the laboratory results or other source documents prior to submission to the DCC. The RC must write the Patient ID and Patient Initials on all documents where the personal information has been obscured.

### Generic Directions for Completing Case Report Forms

*The following general guidelines are applicable to all CRFs used in this study:*

- Print legibly and clearly
- Always use a ballpoint pen with black ink. Do NOT use pencil or multi-colored ink (green, red, blue, etc)
- Do not use erasers or correction fluid
- If an error is made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated
- Dates must match any source or supportive chart, lab, or evaluative documentation. The approved format for collecting dates is Month / Day / Year. If only partial dates are available, write in the known data and supply "UK" for unknown dates. For example, if a participant answers "June of 2007", but cannot recall the exact day, enter 06 / UK / 2007

- Times are collected in standard (12-Hour AM & PM) and military (24-Hour) clock formats. The CRFs will specify which collection method is being utilized. If only a partial time is available, write in the known data and supply “UK” for the unknown units of time. For example, if a participant answers “a little after 4PM”, but cannot remember the exact amount of minutes, enter 04:UK PM (12-Hour) or 16:UK (24-Hour) clock
- Always use patients’ initials, not full name. In cases where patient has no middle initial, please use an “X”
- Avoid using abbreviations
- Be clear, concise, and to the point when completing CRFs, writing comments, or providing additional / supportive information
- Provide signature and date as required on forms
- Do not write comments in the margins or on the reverse side of the CRFs
- Completely fill in study information at the top right corner of each CRF
- After the informed consent process, the Coordinator will assist the patient in responding to a series of questions regarding aspects of his / her OSAS, demographic information, medical history (including present and previous treatment histories), etc.
- Where possible, the RC will maintain a set of original blank CRFs to make copies when needed; or will download and print the necessary CRFs from the DMS prior to the participant’s scheduled clinic or telephone visit.

## Types of Forms

There are two types of forms available through the Data Management System:

**DATA CRFs** contain participant data and are entered into the database – these include Clinical, Surgical, Neuropsychological, and Parent / Guardian / Child Completed forms.

**ADMINISTRATIVE CRFs** are used for processing CRFs, data entry, etc.

\*\* See DATA and ADMINISTRATIVE CRF Table for a comprehensive listing of CRFs and directions for completion \*\*

## General Information

The RC will verify the CRFs and create a visit packet based on the information contained in the corresponding to the arm assignment and listed on the Visit Schedule before the patient’s scheduled visit.



- **CRF Headers** are in the top margin of each CRF and the fields are filled in to match CRF data with the Participant ID. These fields are:

<b>Visit:</b>	A 2-digit alpha-numeric code or a hard-coded visit name, which signifies the visit sequence for the CRF data being collected. This field is located in the center of the CRF header.
<b>Participant ID (PID):</b>	A 6-digit number, that is a unique identifier for each study participant, is written on all study documents and specimens.
<b>Patient Initials (Initials):</b>	An alphabetic code representing the initials from the patients' first, middle, and last name. Use the letter "X" if the participants' middle initial is unavailable. Serves as a check on the ID number and as a quality control check on CRFs.
<b>Site:</b>	Each participating Clinical Center is assigned a unique 2-digit site code number.
<b>RC IDs:</b>	A 4-digit number, representing the site and a unique identifier used to identify the person who completed the form. Serves as a check on the data gathered and as a quality control check for CRFs.
<b>NP ID:</b>	A 4-digit number, representing the site and a unique identifier used to identify the person who administers the form. Serves as a check on the data gathered and as a quality control check for CRFs.
<b>Surgeon ID (located within the body of Surgical CRFs - only):</b>	A 4-digit number, representing the site and a unique identifier used to identify the person who completed the surgical data. Serves as a check on the data gathered and as a quality control check for CRFs.

- The Participant ID (PID) is assigned from the PTLOG. The PIDs are hard-coded for each site on the PTLOG, if your site needs more PIDs assigned; contact the DCC for more participant identification numbers.
- For those forms, given to the parents to complete, the RC will fill in the header information (except for the RC ID, NP ID, or Surgeon's ID) prior to giving the CRFs to the parent to complete.
- The participant should be reassured that confidentiality is maintained on all collected data, throughout the course of the study.
- Questions should not be left unanswered. If a participant chooses to leave a question blank, write "ND per participant's choice", date and initial next to the blank question.
- Participants should be urged to use their "best estimate" rather than leaving the question unanswered. However, exercise caution that you do not paraphrase or answer questions on the participants' behalf.
-

- Even though medical / chart information may contradict participants' response, RCs must not alter participant responses on Parent Completed CRFs.
- The participant is reminded of the follow-up telephone and clinic visits and procedures for the duration of their participation.
- The RC will review all of the CRFs for inconsistencies and missing information **before** the participant leaves the area, and will attempt to collect any missing data.
- An error by the RC, NP, or parent / guardian on the CRFs will be corrected by crossing out the error with a single line in **blue or black ink**, and entering the correct information. The correction **must** be initialed and dated. The correct response *may* be circled for clarification, if necessary.
- A **FORM NAME** is located in a box in the bottom right corner of the page; this is an abbreviation of the form name and is used in structuring the Data Management System (DMS).
- Each CRF is dated and identified with a version number, located in the bottom left corner. This number is important should a CRF become revised at a later date. Pay close attention to this version number, should it change for any given form you will be provided with the new version number.

## Case Report Form Completion

CRFs may be completed by various individuals as follows:

- Parent / Legal Guardian Completed
- Child Completed
- Research Coordinator, Neuropsychologist, or Principal Investigator Completed
- A combination of the above.

To avoid transcription errors the unblinded research coordinator (when applicable) will verify the information for completeness, and query the parent/legal guardian/other if the information is inconsistent or confusing. Under no circumstances shall the child/parent/legal guardian take the questionnaire home to complete. The research coordinator may need to assist in the completion of these forms, if applicable.

### Parent / Guardian Completed CRFs

- "Parent / Guardian" completed forms are completed by the parent / guardian of the child.
- If the parent / guardian make any mistakes they should be instructed to draw a line across the error response, initial and date next to the error to indicate who made the error correction and when it was made. The correct response should be written legibly above or near the original response.
- If the RC or other designated site staff believes that the parent / guardian may have trouble reading the CRFs, the RC may read the questions to the patient but should not answer or complete the CRFs for the parent / guardian.
- When the parent / guardian returns the CRFs, check them for completeness. After the CRFs are reviewed, the RC will complete the RC ID (NP will complete the NP ID, etc) in the top right corner of the master heading of the CRF.

## Child Completed CRFs

- “Child” completed forms are completed by children age 5.0 - 9.99. If any assistance was given to the child while they completed the form mark the appropriate question, indicating that assistance was provided.
- If the child makes any mistakes they should be instructed to draw a line across the error response, initial and date next to the error to indicate who made the error correction and when it was made. The correct response should be written legibly above or near the original response.
- When the child is finished with the CRF, check it for completeness. After the CRF is reviewed, the RC will complete the RC ID (NP will complete the NP ID, etc) in the top right corner of the master heading of the CRF.

## Research Coordinator, Neuropsychologist, Surgeon or Principal Investigator Completed CRFs

- Research Coordinator (RC), Neuropsychologist (NP), Surgeon (SU) or Principal Investigator completed CRFs can be administered to the parent by the appropriate questioner by interviewing the parent / guardian / child; or the information can be gathered from clinical, neuropsychological, or surgical study methods.
- When soliciting information from the parent / guardian / child, the RC, NP, SU, or PI will attempt to get a reasonable answer from the parent / guardian / child if their answer is unclear, incomplete or irrelevant, by repeating the question and refocusing and redirecting the patient, and using the “probing” technique.

Some samples of “probing” techniques that are useful when attempting to broker information from participants:

- **Basic Probe:** Repeat the question to get the participant back on track; this technique can be used when the participant is “going off on a tangent”.
- **Explanatory Probe:** Used to get clearer understanding by completing the incomplete statements of the participant. The questioner asks questions like, “Can you give me an example of that?” or “Can you explain that?”
- **Focused Probe:** Used to get particular understanding about a topic. For example, “What type of ... did you use?”
- **Silent Probe:** The questioner maintains silence and waits for the participant to break silence. This type of technique is generally useful when the participant is taking a lot of time to respond or is hesitant to respond.
- **Drawing Out:** Used when the participant has stopped and is not responding. The questioner restates or rephrases the last question or topic (ergo: “So, the question was...” or “What else can you tell me about...”), which helps the participant start talking again.
- The RC, NP, SU, or PI will ask the parent / guardian / child to elaborate or reconsider an incomplete or inappropriate answer without leading the patient or influencing the content of the answer (creating bias in his / her answer).
- Be mindful of sensitive or painful issues for the parent / guardian / child and exercise sensitivity when asking questions.

- Reassure the parent / guardian / child regarding the confidentiality of their response and explain the importance of the question if the parent / guardian / child seem hesitant.
- If the information can be obtained from study methods – BP, anthropometry, lab device, etc – make certain that all answers are completed.

After the CRFs are completed, please check them for completeness and legibility, the RC will complete the RC ID (NP will complete the NP ID, etc).

### Review of Completed CRFs

The RC will...

- Review all CRFs for legibility, accuracy, and completeness prior to entry into the DMS.
- *All CRFs should be entered into the DMS within 48 hours of being received or collected by the RC.*
- Correct any errors with a single line in **black ink**, enter the correct information, and initial and date the change.

## Directions for Completing Study-Specific Case Report Forms

### Pre-Screening & Screening Summary Form

- Pre-Screening & Screening Summary Form is used to gather important statistical information, which will help in the overall understanding, reporting, conducting, analysis, and interpretation of the data being collected for the CHAT study.
- Prescreening & Screening Summary form should be filled out and entered bi-weekly. It is the sites responsibility to provide Quality Control and Quality Assurance on the numbers being provided and reported.
- These bi-weekly numbers represent the **site level** – ergo: all the participants contacted for those two weeks by site staff.
- For questions 1a-1e, make sure patient contacts are recorded once and only once. The options provided are general and mutually exclusive. For example, if a participant is contacted for participation based on their PSG test score, they would count as a “participant recruited through clinic referral”. If a participant is contacted based on chart review and ENT evaluation, select the method that best describes how they were obtained – it could be “participant recruited through chart review” or “participant recruited through clinic referral”. Make certain that you are counting individuals only once and choosing the most appropriate means of contact.

### Administrative Forms

- Administrative forms do not get entered into the DMS.
- Administrative forms are primarily used for QC / Administrative purposes, and in some cases will need to be submitted to the appropriate committee / individual for review – SURLOG, NPAB, etc.
- Administrative forms are designed to help manage different aspects of study administration.
- Some of the administrative forms contain private and confidential participant information – such as name, address, contact numbers – and should be kept in a secure location. These forms should never be submitted to the DCC.

## Data Entry / Site Staff Completed Forms

- Data Entry / Site Staff Completed forms are used to gather valuable Primary and Secondary endpoint data, safety data, and efficacy data. It is vital to ensure that all questions are answered in their entirety prior to being entered into the DMS.
- Data Entry / Site Staff Completed forms can be divided into 3 major data collection areas: Clinical Forms, Surgical Forms, and Neuropsychological Forms.
  - *Clinical Forms* – used to capture Concomitant Medications, Adverse Events, Eligibility, Blood Pressure, Anthropometry, Physical Examinations data, Venipuncture, Randomization, etc. These forms will need to be completed by an RC and / or PI.
  - *Surgical Forms* – used to capture Pre-Operative, Intra Operative, Post Operative, and Reevaluation data. These forms will need to be completed by the Surgeon and / or RC.
  - *Neuropsychological Forms* – used to capture data from Neuropsychological Test Validity Form, VMI, NEPSY, NEPSY-II, DAS-II, Conner's, WRAML-2, Purdue Pegboard, CBCL, BRIEF, and CDI. These forms will need to be completed by an NP and / or RC.
- Data Entry / Site Staff Completed forms should be kept confidential among site staff members. Some of the data being collected is blinded, and should only be seen by the unblinded Research Coordinator.

## Parent / Guardian / Child Completed Forms

- Parent / Guardian / Child Completed forms are used to obtain self-report demographic, behavioral, and general health information.
- Research staff should be available to answer any questions a parent / guardian / child may have while they are completing the CRFs. Do not paraphrase the questions nor answer the questions for the parent / guardian / child.
- Encourage the parent / guardian / child to complete the CRFs in their entirety. Once a form has been returned, check it for consistency, completeness, and legibility. Try to get any blank answers completed before the parent / guardian / child leaves the clinic.

## Data Management System (DMS) Users Guide

### Introduction

The data management system (DMS) has been developed in accordance with specifications approved by the study investigators for the CHAT project.

To use the DMS, the user will need a computer with an internet browser and access to the internet. The computer will also need to meet the following requirements:

- High speed internet connection.
- Internet Explorer version 6 or 7.
- Communicate in http protocol – port 80 and https protocol – port 443 [consult your local IT].
- User should have administrative rights to machine to download and install web browser plug in.
- Adobe .pdf viewer.

## Starting the Data Management System

The Data Management System (DMS) will have two iterations, a testing / training database and a production database. Users will only be provided with access to the production database after they successfully complete a training and certification exercise within the testing / training database. To start either version of the DMS, the user will run a web browser while connected to the internet. Once the web browser is up, the user will connect to the secure web site that hosts the DMS.

## Entering the Testing Database

For access to the testing / training database, the user will navigate to the following address: <https://rt4.cceb.med.upenn.edu/forms/frmservlet?config=CHAT>.

Once the user navigates to the appropriate web address, the DMS will take a few moments to load (1 to 3 minutes), depending on the users internet connection. Once the system has loaded, the user will be present with a login window. The user will enter their USERNAME, PASSWORD, and the name of the DATABASE into the login screen.

*Note:* The Testing database name is – dev.

After entering a valid username, password, and database, the user will be presented with the main menu for the DMS.

*Note:* Both the Testing and Production databases are similar in design and operability. The major difference is users will have the ability Edit Data in the Testing database; whereas data in the Production database can only be edited for a 24 hour period by the user. Any edits occurring outside the 24 hour editing window will need to be communicated directly to Clinical Data Management (CDM) at the DCC – see below for Discrepancy Management for further details.

All users will be provided with a temporary username and password for the Testing database. After the user has successfully entered a series of Case Report Forms (CRFs), and had their entries scored for accuracy by CDM staff; the users will be provided with their permanent and unique log-on credentials and a certification for their study file.

### Usernames, Passwords, and Electronic Identity

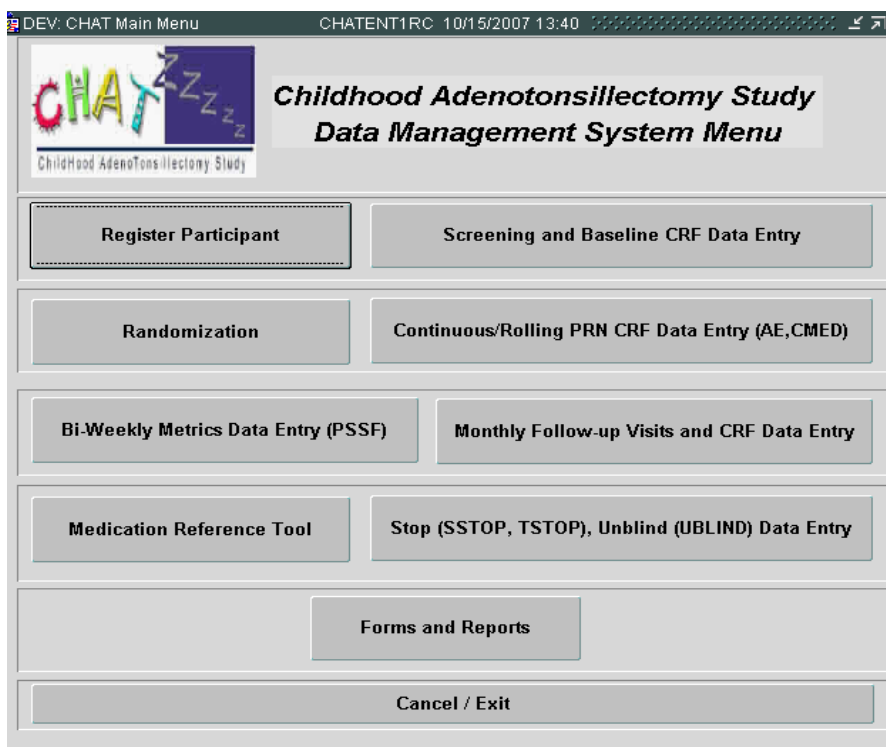
Proper use and management of usernames and passwords are vital to assure that only authorized personnel have the ability to access study data. Users should never, under any circumstances, share their unique Usernames or Passwords with any other study personnel. The Username and Password are log-on credentials, which electronically identify the user. Any

activity within the database is recorded within the audit trail and is linked by the user's unique log-on credentials.

Some users are blinded to specific study information – such as randomization – and only specific site personnel will have access to this module within the DMS. Users should never show confidential electronic data housed within the CHAT database to other study members at their institutions or sites. Such breaches of security undermine the integrity of study data and ultimately affect the population being studied and reported on.

## Main Menu

The main menu, for both instances of the database, is a screen that contains a set of buttons that will provide access to the various sections of the Data Management System (DMS). Below is a listing of each button and a brief description of its function.



### Register Participant

This button provides access to the module that will allow the user to register a participant for the CHAT study.

### Screening and Baseline CRF Data Entry

This button provides access to the module that will allow the user to enter electronic Case Report Forms (CRFs) for the Screening and Baseline CRFs into the DMS.

### Randomization

This button provides access to the module that will allow the user to Randomize study participants into a study arm, after their Screening and Baseline data have been entered into the DMS.

### Continuous / Rolling PRN CRF Data Entry (AE, CMED)

This button provides access to the modules that allow the user to enter the electronic Case Report Forms for Adverse Events (AE) and Concomitant Medications (CMED) for individual participants within the DMS.

### **Bi-Weekly Metrics Data Entry (PSSF)**

This button provides access to the module that will allow the user to enter the Bi-Weekly Pre-Screening and Screening information for their site. *Note:* This is the only form within the database that is Comprehensive Site data, which is collected and summarily reported bi-weekly throughout the recruitment period of the CHAT study. This form is not used to collect individual, participant based information.

### **Monthly Follow-up Visits and CRF Data Entry**

This button provides access to the module that allows the user to enter electronic CRFs for all the study visits occurring after Randomization into the DMS.

### **Medication Reference Tool**

This button provides access to the module that allows the user to look-up medications and their associated coding for use in reporting medications on the CMED form.

### **Stop (SSTOP, TSTOP), Unblind (UBLIND) Data Entry**

This button provides access to the module that allows the user to enter electronic CRFs for the Study Stop (SSTOP), Treatment Stop (TSTOP), and Unblinding of Participant (UBLIND) CRFs.

### **Forms and Reports**

This button provides access to the module that allows the user to run standard reports developed for the CHAT study. This button also allows the user to access blank, downloadable, and printable .pdf files of all study Case Report Forms (CRFs). The unblinded Research Coordinator can access and print Participant's Individual Visit Schedules.

### **Cancel / Exit**

This button will allow the user to exit and log-out of the DMS. Remember to always log-out of the system when you are finished using the DMS.

## **Function of DMS Module**

### **Register Participant**

This module provides the user with the capability to register a participant into the Data Management System (DMS).

To register a participant, enter the Participant Identification Number (PID) into the field labeled "Participant ID". Enter the Participant Initials (Initials) into the field labeled "Participant Initials". Enter the site number, or select it from the drop down menu in the field labeled "Site". Once all three pieces of information have been entered, the user will press the button labeled "Verification". After pressing the button the user is prompted to re-enter the three pieces of information. The user then must press the button labeled "Register". If the second entry matches the first entry, a message will be displayed indicating that the registration was successful. However, if any field from the second entry does not match first entry; a message will be displayed indicating which field does not match. The user will then be required to correct the error. This process is done to ensure that Data Entry Errors do not occur when registering a Participant. Pressing the "Cancel" button will exit the user back to the main menu.

*Note: Users can either tab between fields or click on a specific field anywhere within the DMS as a way to navigate from field to field.*

### **Screening and Baseline CRF Data Entry**

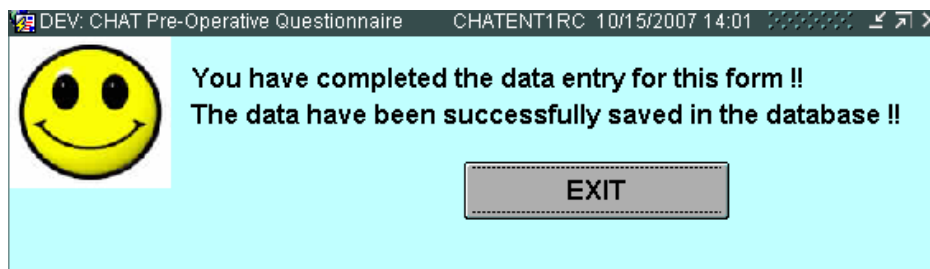
This module gives the user the ability to electronically enter visit and Case Report Form (CRF) data into the Data Management System (DMS) for those forms associated with the Screening and Baseline data.

After clicking on the Screening and Baseline CRF Data Entry button, users will be taken to a selection window, where they will be required to enter the Participant ID. Users will then enter a



Visit Code by clicking on the little grey box to the right of the white field. Once a visit code has been selected, users will need to enter a CRF date. This field will need to be re-entered for verification purposes. The user will then either enter the site or type in their site number. Users will then be required to enter either the RC ID or NP ID, which corresponds to the header of the CRF they are entering. The RC ID or NP ID will need to be re-entered for verification purposes. The last field that will need to be completed is the Available CRFs. Users will click on the little grey box to the right of the white entry box and a table of available forms for the visit selected will be displayed.

After selecting the desired form, users will need to click on “Enter CRF”. The user will be taken into the electronic CRF and can begin data entry. After entry has been performed users must press “SAVE”. The system will display the following message:



*Note:* This Smiley Face Message indicates that the data was saved and committed to the CHAT database.

After clicking on the “Exit” button, users will be taken back to Screen and Baseline CRF Selection Menu.

To enter data for a new participant, simply click on the “Clear All” button and the selection fields will be reset to blank. Follow the steps above to enter a new participant and subsequent data.

To leave this menu, click on the “Exit” button to be taken back to the CHAT DMS Main Menu.

## Randomization

This module provides the unblinded Research Coordinator (RC) user with the means to access the Randomization module of the Data Management System (DMS).

Only the Unblinded RC will have access to the Randomization module. To enter data, click on the Randomization button. The Unblinded RC will be taken to the Randomization Menu. The Visit Code and Available CRFs will be pre-populated. The Unblinded RC will need to enter the Participant ID, CRF Date, Clinical Site, and RC ID. The CRF Date and RC ID will need to be entered a second time for verification purposes. After this information has been entered, click on “Enter CRF”.

The Unblinded RC will then be taken to the Randomization electronic Case Report Form (CRF). After entering the data for questions 1-6, the Unblinded RC will click on the RANDOMIZE button. A pop-up window will indicate that a randomization code has been generated. The randomization code will be displayed, after the Unblinded RC clicks on OK. The randomization code, specifically the one digit number, will need to be written on the paper CRF after it has been generated. The Unblinded RC must then click on the “Save Data” button. Once the Smiley Face Message pops up, the Unblinded RC will be prompted to EXIT.

If no Smiley Face Message has been displayed, do not exit out of the form. This means that the Randomization Code was not saved. If you are unable to save, contact the DCC immediately, as the participant is not technically randomized until the Unblinded RC has received a Smiley Face Message.

### **Continuous / Rolling PRN CRF Data Entry (AE, CMED)**

This module provides the user with the means to access and electronically enter PRN Case Report Forms (CRFs) data into the Data Management System (DMS).

After clicking on the Continuous / Rolling PRN CRF Data Entry (AE, CMED) button, users will be taken to the Continuous / Rolling PRN CRF Data Entry (AE, CMED) Menu. This menu is slightly different than other data entry menus within the CHAT DMS. This menu only requires that the Participant ID, Clinical Site, and Available CRFs be entered by the user. After this data has been entered the user will be taken to the participant's continuous / rolling log form for either the Adverse Events (AE) or Concomitant Medications (CMED).

Remember to "Save" data and wait for the Smiley Face Message prior to exiting either the AE or CMED form. For information on CMED coding, refer to items below.

*To code Adverse Events, please consult the following:*

The web-based version of the Common Terminology Criteria for Adverse Events (CTCAE) will give the user information that should be recorded on a paper Adverse Event (AE) form prior to completing data entry in the CHAT DMS interface.

***Important Note: The link below will access a web page independent of the CHAT DMS. This link is maintained by the National Institutes of Health (NIH). Problems arising from connectivity, usage, or performance cannot be addressed by members of the CRCU nor the DCC. Help and Support for this is supplied by NIH via their help menu located on the screen.***

To access the external link for Adverse Event Coding, navigate to:

<http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>

Detailed instructions for accessing the CTCAE online guide were provided to each Research Coordinator (RC) at training. Additional copies are attached to the back of the MOP and can also be obtained by contacting CDM staff at the DCC.

#### **Search CTCAE Dictionary**

- Access the CTCAE Dictionary by logging on to the application and selecting the **Dictionary** tab. By default, the system displays the CTCAE v3.0 search page.
- To display a list of adverse events for a keyword, enter the keyword in the **Search for** field and click the **Literal** button.

This displays a list of adverse events (by short name) as hyperlinks.

### **Bi-Weekly Metrics Data Entry (PSSF)**

This module gives the user the ability to electronically enter the bi-weekly screening metrics for their site into the Data Management System (DMS).

After clicking on the Bi-Weekly Metrics Data Entry (PSSF) button, the user will be taken to the Bi-Weekly Prescreening & Screening Metrics Site Selection Menu. Users will be required to

enter their Clinical Site, Date, and RC ID. Both Date and RC ID will need to be re-entered as a verification method. The Available Form has been pre-populated. After all the necessary data has been entered, users will click on the “Enter CRF” button. They will then be taken to the eCRF for the Prescreening and Screening Form (PSSF) to enter their sites bi-weekly recruitment metrics.

*Note:* This is a summary form that captures data at the site level, and should not be used to enter data for individual participants or potential participants.

After entering the data as outlined in the CRF Completion Guidelines, users will then be required to click on Save. After the Smiley Face Message has appeared, the user can exit this window.

### **Monthly Follow-up Visits and CRF Data Entry**

This module gives the user the ability to electronically enter data for all of the visits occurring after Randomization in the Data Management System (DMS).

After clicking on the Monthly Follow-up Visits and CRF Data Entry button, users will be taken to the Monthly Follow-up Visits and CRF Data Entry menu, where they will be required to enter the Participant ID. Users will then enter a Visit Code by clicking on the little grey box to the right of the white field. Once a visit code has been selected, users will need to enter a CRF date. This field will need to be re-entered for verification purposes. The user will then either enter the site or type in their site number. Users will then be required to enter either the RC ID or NP ID, which corresponds to the header of the CRF they are entering. The RC ID or NP ID will need to be re-entered for verification purposes. The last field that will need to be completed is the Available CRFs. Users will click on the little grey box to the right of the white entry box and a table of available forms for the visit selected will be displayed.

After selecting the desired form, users will need to click on “Enter CRF”. The user will be taken into the eCRF (electronic Case Report Form) and can begin data entry. After entry has been performed users must press “SAVE”. Once the Smiley Face Message has appeared, the user can exit this window and return to the Monthly Follow-up Visits and CRF Data Entry menu.

To enter data for a new participant, simply click on the “Clear All” button and the selection fields will be reset to blank. Follow the steps above to enter a new participant and subsequent data.

To leave this menu, click on the “Exit” button to be taken back to the CHAT DMS Main Menu.

### **Medication Reference Tool**

This module functions as a searchable medical thesaurus, and allows the user to look-up brand and generic named drugs from within the Data Management System (DMS).

After clicking on the Medication Reference Tool Button, users will be taken to into the Medication Reference Tool. See example below:

The screenshot shows a software window with a light gray background. It is divided into three main sections:

- Enter Query Criteria:** This section contains three radio buttons. The first, labeled "Brand Name : ...", is selected. Below it are two text input fields. The second radio button is labeled "Generic Name ..." and the third is "Drug Code: ...".
- Sort Criteria:** This section contains three radio buttons. The first is "Drug Code", the second is "Brand Name", and the third, "Generic Name", is selected.
- Drug Names and Codes:** This section contains a table with three columns: "Drug Code", "Brand Name", and "Generic Name". The table has 10 rows, all of which are currently empty. A vertical scrollbar is visible on the right side of the table.

At the bottom of the window, there are two buttons: "Execute Query" on the left and "Cancel" on the right.

This window is divided by 3 sections:

- Enter Query Criteria – This section allows the user to enter and query for drugs based by either Brand Name, Generic Name, or Drug Code.
- Sort Criteria – This section allows the user to sort their query entry by Drug Code, Brand Name, or Generic Name.
- Drug Names and Codes – This section displays the data queried and sorts it based on the criteria entered by the User.

To search medications by Brand Name, make sure the radio button next to **Brand Name** has been selected, then enter the text of the drug to be searched for, and click on the button **Execute Query**. In the example below we are searching for aspirin:

Enter Query Criteria

Brand Name : ... Aspirin

Generic Name ...

Drug Code: ...

Sort Criteria

Drug Code  Brand Name  Generic Name

Drug Names and Codes

Drug Code	Brand Name	Generic Name
11791	ASPIRIN WANTACID	ASA/CALCIUM CARB/MAG/AL HYDROX
11791	ASPIRIN TRI BUFFERED	ASA/CALCIUM CARB/MAG/AL HYDROX
1820	ASPIRIN LOW DOSE	ASPIRIN
1820	ASPIRIN SR	ASPIRIN
1820	ASPIRIN LOW-STRENGTH	ASPIRIN
1820	ASPIRIN	ASPIRIN
1820	ASPIRIN EC LOW DOSE	ASPIRIN
1820	ASPIRIN LITE-COAT	ASPIRIN
1820	ASPIRIN ENTERIC COATED	ASPIRIN
1820	ASPIRIN EC	ASPIRIN

Execute Query

Cancel

After the query has returned results, use the scroll bar to search the list for the most appropriate drug name.

Then write the code down on the Concomitant Medication Log. This information will then be used to enter the Medication code into CHAT DMS.

Repeat this search as need, based on the medications recorded during the clinic visit. If Brand Name is not working as query, try searching the term using the Generic Name query.

To search medications by Generic Name, make sure the radio button next to **Generic Name** has been selected, then enter the text of the drug to be searched for, and click on the button **Execute Query**. In the example below we are searching for aspirin:

**Enter Query Criteria**

Brand Name : ...

Generic Name ... Aspirin

Drug Code: ...

**Sort Criteria**

Drug Code  Brand Name  Generic Name

**Drug Names and Codes**

Drug Code	Brand Name	Generic Name
1820	BAYER	ASPIRIN
1820	ANALGESIC	ASPIRIN
1820	BAYER EXTRA STRENGTH	ASPIRIN
1820	ECO-5	ASPIRIN
1820	ADULT LOW STRENGTH ASPIR	ASPIRIN
1820	LOW-DOSE ASPIRIN	ASPIRIN
1820	<b>ASPIRIN</b>	<b>ASPIRIN</b>
1820	BAYER ARTHRITIS PAIN REGIMEN	ASPIRIN
1820	BAYER CHILDREN'S ASPIRIN	ASPIRIN
1820	ASPIRIN LOW-STRENGTH	ASPIRIN

**Execute Query** **Cancel**

After the query has returned results, use the scroll bar to search the list for the most appropriate drug name.

Then write the code down on the Concomitant Medication Log. This information will then be used to enter the Medication code into CHAT DMS.

Repeat this search as need, based on the medications recorded during the clinic visit.

To look up, or verify that the correct Drug Code was used, make sure the radio button next to **Drug Code** has been selected, then enter the code number of the drug to be searched for, and click on the button **Execute Query**. In the example below we are searching for 1820:

**Enter Query Criteria**

Brand Name : ...

Generic Name ...

Drug Code: ... 1820

**Sort Criteria**

Drug Code  Brand Name  Generic Name

**Drug Names and Codes**

Drug Code	Brand Name	Generic Name
18205	CLINIMIX E	AA 5%/CAL/ELECTROLYTE-TPND20W
1820	LOW DOSE ASPIRIN	ASPIRIN
1820	BAYER	ASPIRIN
1820	ANALGESIC	ASPIRIN
1820	BAYER EXTRA STRENGTH	ASPIRIN
1820	ECO-5	ASPIRIN
1820	ADULT LOW STRENGTH ASPIR	ASPIRIN
1820	LOW-DOSE ASPIRIN	ASPIRIN
1820	<b>ASPIRIN</b>	<b>ASPIRIN</b>
1820	BAYER ARTHRITIS PAIN REGIMEN	ASPIRIN

**Execute Query** **Cancel**

After the query has returned results, use the scroll bar to search the list for the most appropriate drug name.

Repeat this search as often as need to look up drug names based on a code number, or to verify that a number correctly matches a drug name.

## Stop (SSTOP, TSTOP), Unblind (UBLIND) Data Entry

This module will allow users to electronically enter the data collected on the Study Stop (SSTOP), Treatment Stop (TSTOP), and Unblinding of Participant (UBLIND) forms within the Data Management System (DMS).

After clicking on the Stop (SSTOP, TSTOP) Unblind (UBLIND) Data Entry button, users will be taken to the Participant Study Stop, Treatment Stop and Unblind menu, where they will be required to enter the Participant ID. Users will then enter a Visit Code by clicking on the little grey box to the right of the white field. Once a visit code has been selected, users will need to enter a CRF date. This field will need to be re-entered for verification purposes. The user will then either enter the site or type in their site number. Users will then be required to enter either the RC ID or NP ID, which corresponds to the header of the CRF they are entering. The RC ID or NP ID will need to be re-entered for verification purposes. The last field that will need to be completed is the Available CRFs. Users will click on the little grey box to the right of the white entry box and a table of available forms for the visit selected will be displayed.

After selecting the desired form, users will need to click on “Enter CRF”. The user will be taken into the electronic CRF (Case Report Form) and can begin data entry. After entry has been performed users must press “SAVE”. Once the Smiley Face Message has appeared, the user can exit this window and return to the Participant Study Stop, Treatment Stop, and Unblind menu.

To enter data for a new participant, simply click on the “Clear All” button and the selection fields will be reset to blank. Follow the steps above to enter a new participant and subsequent data.

To leave this menu, click on the “Exit” button to be taken back to the CHAT DMS Main Menu.

## Forms and Reports

This module provides the user with the capability to download electronic (.pdf) Case Report Forms (CRFs) for every study visit. This module will give the user the ability to run and view standard reports developed for the CHAT study. This module will also allow the user to access and print participant specific electronic visit schedules.

### Case Report Forms

This module provides the user with the capability to view and print electronic CRFs in the form of Visit Packets or individual CRFs. Paper CRFs for data entry for the CHAT study are provided from this button electronically in .pdf format. The most current versions of the CRFs are readily available throughout the duration of the study on the CHAT Production DMS.

*Case Report Forms:* This button will allow users to access the individual electronic copies of the Case Report Forms. After clicking on this button, users will be taken to a sub-menu with the following options:

- *Administrative CRFs:* This button will allow users to access and print individual administrative CRFs for use in the daily administration of study visits, procedures, and collection of confidential participant information. Administrative CRFs are never entered into the DMS.
- *Data CRFs:* This button will allow users to access and print individual data CRFs for use in the collection of study data based on type of procedure, clinic specialization, or self-report participant information.
- *EAT CRF Visit Schedule:* This button will allow users to access and print the CRF Visit Schedule for EAT, which outlines all of the CRF collection points for each visit.
- *WWSC CRF Visit Schedule:* This button will allow users to access and print the CRF Visit Schedule for WWSC, which outlines all of the CRF collection points for each visit.
- *Visit Packets:* To access and print visit packets, click on the button with the name of the visit you wish to print (see the DMS visit schedule below). These packets have been compiled, based on the data expected to be collected at a given visit. After the Randomization visit, the packets are arraigned based on the participants study arm. The arraignment of randomization arm study packets will not affect blinding for this study, as the visit packets are blank.
- *Participant’s Individual Visit Schedules:* This button will allow the unblinded Research Coordinator (RC) to access and print individual visit schedules based on randomization. These visit schedules list out the visit window for each visit occurring after the participant has been randomized. This listing will show open window dates (-7 days), target dates, and close window dates (+7 days) for all of the participant’s subsequent visits after randomization. To print an individual visit schedule, open the module and enter the PID. The system will automatically populate Initials, Clinical Site, Randomization Date, and



Randomization Arm. Clicking on the Proceed button will generate the visit schedule for the PID entered. This visit schedule can then be printed, but should be maintained in a secure area. Once printed this visit schedule contains Blinded information and should not be shared with any other site / staff members.

<b>CHAT Data Management System (DMS) Visit Reference Guide</b>			
<b>Visit Name</b>	<b>Visit Number</b>	<b>Visit Code</b>	<b>Time</b>
Screen	1	Screen	Day -30 to -1
PSG	2	Screen	Day -30 to -1
Baseline	3	Baseline	Day -30 to -1
Rand	4	Rand	Day 0
Surgery	5	T1	Month 1 (M1)
Phone Contact	6	V1	Month 2 (M2)
Clinic Visit	7	V2	Month 3 (M3)
Phone Contact	8	V3	Month 5 (M5)
PSG	9	V4	Month 6 (M6)
Endpoint	10	V5	Month 7 (M7)
ENT Reeval	11	T2	Month 8 (M8)

**Note:** When writing the Visit Number in the header of the CRF (see example below), please refer to the column above titled **Visit Number**. The CHAT Data Management System will provide all of the information listed above when a user is selecting a Visit Number.

C  
H  
A  
T

CHILDHOOD ADENOTONSILLECTOMY STUDY  
Physical Examination  
Visit 07

Participant ID: 123456  
Participant Initials: ABC  
Site: 99  
Date: 09/27/2007  
RC ID: 99-99

In this example of a Physical Examination (PE2) form, the Visit Number recorded is 07. This corresponds to a Clinic Visit, Visit Number 7, Visit Code V2, and Time point M3.

## Reports

Standard reports will be developed, reviewed and generated by the Data Coordinating Center on a monthly basis for distribution and review by the Data Safety and Monitoring Board and the Steering Committee.

## Discrepancy Management

Data entered into the CHAT Production Data Management System (DMS) can be edited by site staff for a period of 24 hours after the initial entry has occurred. This 24 hour editing period allows for the correction of data for the purposes of keying mistakes, typos, and general errors associated with the data entry process. After the 24 hour editing period has expired, site Research Coordinators (RCs) will not be able to edit the data entered into the CHAT DMS. Any change after this 24 hour editing period will need to be completed by CDM staff at the DCC.

For the CHAT study, there will be two primary types of discrepancies – System-Generated Discrepancies and Manual Discrepancies.

- *System-Generated Discrepancies* – refer to discrepancies that are triggered by a series of electronically stored validation rules, which will check entered and saved data in the CHAT Data Management System (DMS).
- *Manual Discrepancies* – refer to discrepancies that are manually initiated by CDM or members of the Biostatistics department in response to observed errors / problems witnessed in the reporting or analysis process.

The CHAT study will have a series of validation rules implemented on the electronic data. These validation rules will check for missing data fields, check the consistency of both inter and intra form responses, check for skip pattern inconsistencies, and will be used to verify and clean any data entered into the Production CHAT DMS. These validation rules will check entered and saved data. Any resulting validation error that has been triggered by validation rules will be translated by CDM staff into a series of data queries listed out in an excel spreadsheet (.xls format). The data query spreadsheet will be submitted to the unblinded Research Coordinator (RC) at the beginning of each month for clarification. The DCC will send the query spreadsheet via email requesting clarification or action on those discrepant fields which have triggered a validation error. It is the unblinded RC's responsibility to respond to the queries via email and provide a resolution in the column labeled "Resolution" on the query spreadsheet.

Queries will require the unblinded RC to check the paper Case Report Forms (CRFs) and / or contact the participant in order to obtain a resolution. Some queries may not be resolvable and, in those rare cases, the unblinded RC would simply reply to the query by marking it as "UNRESOLVABLE". Queries will require that the paper documents be updated, augmented, or corrected. Data being corrected on the paper documents should be clearly marked. Any errors should have a single line drawn through the error with the correct answer, the date of change, and the initials of the person making the change clearly written beside or near the field determined to be in error. After the query resolutions have been returned to the DCC by the unblinded RC, members of CDM staff at the DCC will update the database accordingly.

After the 24 hour grace period, corrections to data entered into the Production Database of the CHAT DMS can only be performed by CDM staff at the DCC upon receipt of a query resolution. Corrections can also be made by CDM staff when a written request to change incorrectly entered and saved data within the CHAT DMS has been received. To request a correction of a data field that has been entered in error, the unblinded RC will submit a Change Request via

email. The Change Request will clearly identify the Participant, Visit, Field to be changed, and Reason why the change is being requested.

In all cases, the data on the paper CRFs must match the data entered into the CHAT DMS. As a check of this, periodic Data Quality Inspections (DQIs) will be conducted by CDM staff from the DCC – see below for a detailed explanation of Data Quality Inspections.

## **Data Integrity**

This section will address Data Integrity, Audit Trails, and Data Quality Inspections. These three items will be used in conjunction to ensure the quality, reliability, and accuracy of CHAT study data.

Electronic data entered into the Production Database of the CHAT Data Management System (DMS) using the data captured on the paper Case Report Forms (CRFs) relies on User Authentication (log on credentials – Username and Password) to delineate the identity of the person accessing the DMS during a given entry session. Access to the Production Database of the CHAT DMS will only be granted to those individuals who have successfully completed the training / certification process as administered by CDM staff at the DCC.

The data collected on the paper CRFs should be checked for completeness and clarity prior to data entry. The CHAT Production Database is a single-entry data management system. Any data errors – unintended or violations of validation rules – can only be augmented by CDM staff at the DCC, and then only after appropriate documentation has been provided by the unblinded RC.

To ensure the validity of the study results and of the data collected at the clinical sites, it is crucial to minimize the opportunity for data corruption via accidental or intentional manipulation of the CHAT DMS. As a result it is critical that mechanisms for data access, data use, and data accountability are put in place at the Clinical Sites to assure the integrity of all CHAT data.

## **Audit Trail**

Paper CRF documentation of the data collected during the course of the study are the primary means of constructing an audit trail. The purpose of an audit trail is to trace back the electronic data collected in the DMS to the source from which it was obtained as a means to document the integrity of the data and therefore of the study conduct and results. It also lends to protecting the safety of the study participants and potentially the safety of the participant population affected by the outcome of the study results.

Data Integrity can only be assured when an audit trail accurately portrays who, what, when, where, and why study data were entered or modified. Clinical Sites must employ a system to assure that study staff are aware of their responsibilities in protecting data integrity and have a defined means to document any changes or modifications made to the data.

If any variation from standard operating procedures or working practices relevant to data integrity at a Clinical Site occurs during the conduct of the study, the instance(s) should be clearly documented. This documentation must be maintained with other study documents and should be clearly communicated with Project Management at the DCC. Bear in mind that gross violations of data integrity ultimately affect the study population, which can be affected by the final outcome of the CHAT study results.

## Data Quality Inspections (DCC)

Data Quality Inspections (DQIs) are utilized by CDM staff at the DCC when source documents are entered and stored at a remote location. CDM staff at the DCC will perform regular inspections of copied CRFs provided by the CHAT Clinical Sites on a random sample of CRFs for the CHAT study. CDM staff at the DCC will provide a list of CRFs per Participant Identification Number to each Clinical Site at the time of a DQI. The Unblinded RC at the clinical sites will ensure that sensitive data (such as participant name, address, private data, etc) of the participant's is not included prior to submitting the requested CRFs to the DCC for inspection. The total number of records to be sent for each visit will be 10% of the total entered visit packets for randomized participants in the CHAT study and will be limited to those forms that directly impact primary and secondary analysis.

Steps involved in the DQI:

1. On a yearly basis, CDM staff at the DCC will request copies of the paper CRFs from the Clinical Sites for a list of randomly selected records for a specified set of visits.
2. The Unblinded RC at the Clinical Site will forward copies of the CRFs to the DCC via courier.
3. A CRF-to-database comparison of each CRF page will be conducted. Each field will be checked for accuracy to ensure that data were entered and transferred correctly.
4. Any errors identified during the DQI will be reconciled through manual queries between CDM staff at the DCC and the Unblinded RC at the Clinical Site. An error rate of greater than 5% may require that other measures – such as retraining, further inspection of data, site visits, etc – be taken to correct the errors and help to ensure fewer errors in the future.
5. A detailed DQI report of error rates will be provided to the CHAT Steering Committee as well as the Clinical Site.

*Refer to Specialty MOPS for Quality Control Procedures related to collecting data.*

## Database and System Maintenance

Routine maintenance for the CHAT database server and client systems should be infrequent. Any routine maintenance of the CHAT database will be scheduled. Notification will be provided by either Information and Systems Technology (IST) personnel or Software and Systems Development (SSD) personnel from the CRCU at the DCC. Notification will be provided using email or via direct contact. Maintenance documentation and tracking will be conducted as a specific part of this project to ensure Network Security.

Software maintenance will be performed when modifications are requested due to programming errors or application enhancements. Changes to software will be batched together where possible to minimize disturbance of system availability. System Users will be notified of impending software changes by either IST personnel or SSD personnel from the CRCU at the DCC. Revalidation of affected systems will be performed when any changes with the CHAT database, servers, and / or client systems occur.

## Disaster Recovery

In the event of a disaster IST personnel at the DCC will manage the planning, prioritizing, and directing of DCC functions and operations to ensure the recovery of data files or software. All

study wide entities with pertinent study information at their site (electronic or paper copy), must identify a plan for the re-creation of the study data following a partial or complete study data loss.

## CHAT DCC Helpdesk

Helpdesk Phone Number: 215.573.4623

Helpdesk E-mail: [crcuhelp@mail.med.upenn.edu](mailto:crcuhelp@mail.med.upenn.edu)

The CHAT helpdesk will be available at the DCC from 9am – 5pm EST Monday through Friday. The helpdesk can be reached via telephone or e-mail using the contact information above. If contacting helpdesk via telephone, you will be prompted to leave a message indicating the nature of your support requested. Your message will be saved electronically and forwarded to helpdesk support personnel, who will review your message and contact you as soon as possible (typically within an hour). E-mails will be handled in a similar fashion. Each helpdesk support staff member will receive a copy of e-mails sent to the helpdesk e-mail address, and will respond as soon as possible.

Support requests that are submitted after 5pm EST will be addressed first thing the following morning.

Requests to the helpdesk should be limited to technical support of the CHAT Data Management System (DMS) as it pertains to the CHAT study. This would include any issues involving connectivity / access to the CHAT DMS, installation on your computer, Error Messages, etc. Questions related to general study operation or the protocol, or other technical issues that are not directly related to the CHAT DMS should be directed to Project Management (PJM) or Clinical Data Management (CDM) at the DCC.

## Core Centers Role in Quality Assurance

### Data Coordinating Center (DCC) – University of Pennsylvania

*The Data coordinating Center Responsibilities include:*

- Overall leadership regarding study design and conduct of the clinical trial.
- Preparation and distribution of the study protocol and Manual of Procedures (MOP) based on collaboration with the Steering Committee and the NHLBI.
- Collaboration with other study investigators in the development, testing, and use of all CRFs and study procedures.
- Provision of an efficient data management system (**DMS**) to enter data directly into the central database at the DCC, and to implement single data entry with verification.
- Development and application of quality assurance procedures including data tracking and validation, query processes, and maintenance of related documentation.
- Development of tracking and storage procedures for laboratory samples.
- Training of clinical site staff and coordination of the site monitoring.
- Coordination of Steering Committee meetings.
- Preparation of detailed reports regarding participant recruitment and retention, data collection activities, and interim results to the Steering Committee and DSMB.

- Collaboration with study investigators in the analysis and publication of study results.

## **Neuropsychology and Surgical Cores – University of Michigan**

The University of Michigan provides oversight and quality control assurance for neuropsychological and surgical related procedures/conduct for the study. These two core centers are overseen by Ron Chervin, MD.

### **NP Quality Assurance Core (NPQA)**

The Neuropsychological Quality Assurance Core is directed by Bruno Giordani, PhD. Please refer to the NP Manual of Procedures for details on test administration and certification of staff on CHAT-related NP instruments.

### **Surgical Quality Control Core (SQCC)**

Dr. Garetz from the University of Michigan will direct the Surgical Quality Control Core, and also serve as the central coordinator for the surgical portion of the study. Dr. Witsell from Duke University will serve as an outside ENT consultant and will advise on surgical quality control as well. The University of Michigan and Duke University will not be participating sites for patient recruitment, thus eliminating any possible institutional bias. Dr. Garetz will be responsible for standardization of surgery and documentation of techniques, perioperative care, and complications, and will oversee protocol development and amendments for the surgical intervention. Also, on an ongoing basis, The SQCC will facilitate communication and development of consensus among otolaryngologists at all sites regarding Adverse Events and other issues related to surgery and quality control.

### **Surgical Subcommittee**

The surgical subcommittee is comprised of the chair and lead otolaryngologists from each of the participating sites, as well as a member of the DCC. The subcommittee will meet on a monthly basis initially and/or as needed to discuss adverse events related to surgery and quality control issues. Annually, the members will meet at the American Academy of Otolaryngology-Head and Neck Surgery, and at periodic Steering Committee meetings for ongoing protocol and operations review.

To monitor surgical efficacy, the surgeon will complete data sheets on each patient at the time of surgery documenting surgical technique, size of tonsils and adenoids pre-operatively, whether or not tonsils were entirely removed and degree of residual adenoid obstruction post-operatively as well as any intra-operative complications.

### **Quality Assurance related to Adenotonsillectomy**

For quality assurance, intra-operative photographs will be obtained on a 10% sample. Using a mouth-gag to optimize visualization, non-magnified digital photos of the oro-pharynx before and after tonsillectomy, and of the naso-pharynx with the palate retracted using an angled telescope before and after adenoidectomy, will be obtained.

These pre and post-procedure photographs will be transmitted electronically to a secure, password encrypted computer and examined regularly by a single otolaryngologist at the Surgical Quality Control Core. The photos will also be compared to the data obtained on the intra-operative data sheet to ensure that the grading system is being consistently applied by all surgeons and that adequate tissue removal has been performed. Any noted discrepancies in scoring or inadequate tissue removal will be discussed with the specific institution's lead otolaryngologist within 10 days of photo receipt. If repeated discrepancies in scoring or inadequacy of tissue removal by a particular surgeon or institution are observed despite verbal feedback, a training session will be arranged to review the grading system and surgical

technique using representative photographs (refer to the Manual of Procedures for Surgical Quality Control for detailed information).

Complications resulting from surgery will be documented at each institution with use of an intra-operative data sheet and by reports obtained from the family during interim follow-up, supplemented by medical records, as appropriate. Major or unanticipated adverse events will be reported as required by institutional IRB protocol. Complications resulting from surgery will be documented at each institution and communicated by the site PI to the Surgery Quality Control Core of the DCC. The DCC will report these data to the independent Medical Safety Officer and to the DSMB and NHLBI. Periodically, these results will be tabulated and any significant deviations from reported national rates will be investigated. If any surgical complication is noted that exceeds expectation of usual care, or any site experiences excessive problems (as defined by the SQCC and/or DSMB), Dr Garetz will initiate an investigation and prepare a report for the DCC, DSMB and Steering Committee who will recommend with the Steering Committee recommending actions (with DSMB approval)

### **Scientific Coordinating (SCC) and PSG Reading Centers(PRC) Case Western Reserve University**

**The SCC is directed by Susan Redline and functions to:**

- Provide leadership in directing the scientific (clinical) aspects of protocol development and study implementation
- Provide specific training and technical support related to specialized measures.
- Oversee study governance
- Assist with statistical analyses, providing leadership in areas using complex sleep data
- Provide Core Laboratories for PSG and AMBP through the Polysomnography Reading Center (PRC)

#### **Polysomnography (PSG)**

- Develop procedures and manuals for acquiring and analyzing standardized PSG data across sites using varied PSG equipment;
- Oversee central training of PSG technicians participating in the CHAT protocol
- Score all PSG records, maintaining and documenting high reliability, and transmit these data (including information on PSG study eligibility and urgent referrals) on a timely basis to the CCs and DCC.
- Provide ongoing quality assurance for PSG data, including technical support, assignment of quality codes, and feedback and tracking reports.
- Provide mechanisms for sharing PSG data
- Provide analytic files to the DCC

### **Laboratory of Clinical Biochemistry Research (LCBR) – University of Vermont**

The LCBR will act as the central repository for storage and analysis of blood samples. Samples will be stored locally and shipped to LCBR on a monthly basis for analysis. Sites will alerted if a lab value is out of range and all laboratory data will be transmitted to the DCC where they will be stored. Refer to Appendix D: Laboratory Manual of Procedures for details on Lab collection, processing, storage, shipping and analysis.

## **Maintenance and Disposition of Study Documents, Data and Materials**

### **Distribution**

#### **Internal Distribution of Study Documents**

The DCC is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to this trial. During the conduct of this Protocol, the DCC will be responsible for the distribution of the Protocol, Manual of Operations and Procedures, and study reports to the ICCRN randomization sites. At the end of the study, these documents will be archived by the DCC and forwarded to the National Technical Information Service (**NTIS**). Minutes of all appropriate committee meetings will be maintained in the files at the DCC. At the conclusion of the study, these minutes will be archived and forwarded to the NHLBI.

#### **External Distribution of Study Documents**

The NHLBI will be responsible for the distribution of study documents and manuscripts requested by individuals not associated with CHAT project. Refer to NHLBI Data Sharing Guidelines in Appendix D of the protocol.

#### **Case Report Forms (Data Collection Forms)**

At the close of the study, all CRFs on file at the DCC, without personal identifiers, will be archived and stored at the DCC. The clinical sites will maintain a file on each participant, which will become part of the participant's medical record.

#### **Data Tapes and Analysis of Results**

The DCC will prepare a computer tape of the study data, results, and analyses at the conclusion of the study. This tape will be accompanied by appropriate documentation. One copy will be forwarded to NHLBI and one to the NTIS, U.S. Department of Commerce, Springfield, Virginia so that the information may be generally available, at a small charge, to the scientific community. The DCC will prepare a data tape of analysis pertaining to each major study paper. At the end of the analysis phase, all of these tapes with appropriate accompanying documentation will also be submitted to NHLBI and NTIS. The DCC will provide documentation of all formulas and statistical analyses used in the study or referred to in the study documents. This information will also be made available to NHLBI and NTIS.

#### **Record Retention**

The DCC must maintain all trial records in accordance with their internal standard operating procedures. Clinical sites must maintain all study related materials in accordance to their local IRB guidelines and/or until receiving written notification from the DCC or NHLBI.

#### **Regulatory Compliance and Annual Renewals**

The DCC will coordinate the regulatory requirements needed to carry out the protocol on a continuous basis. Official memos and amendments related to any of the core centers must be sent through the DCC to maintain version control and consistency across sites.

#### **Annual/Continuing Review**

##### **Recommendations to include in Report to Local IRB**

The following is a suggested list of items to include when submitting your annual review to the IRB. Modifications may be necessary based on your institutional guidelines.

- the number of subjects accrued;



- a summary of any unanticipated problems and available information regarding adverse events (in many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document)
- a summary of any withdrawal of subjects from the research since approval or the last IRB review;
- a summary of any complaints about the research since approval or the last IRB review;
- a summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;
- any relevant multi-center trial reports;
- any other relevant information, especially information about risks associated with the research;
- a copy of the current informed consent document and any newly proposed consent document.