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Pediatric Adenotonsillectomy Trial for Snoring (PATS): Protocol for a Randomized Control Trial to Evaluate the Effect of Adenotonsillectomy in Treating Mild Obstructive Sleep-Disordered Breathing

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Abstract

Introduction Mild obstructive sleep-disordered breathing (oSDB), characterized by habitual snoring without frequent apneas and hypopneas on polysomnography, is prevalent in children, and commonly treated with adenotonsillectomy (AT). However, the absence of high-level evidence addressing the role of AT in improving health and behavioral outcomes has contributed to significant geographical variations in care and potential for surgery to be both over- and under-utilized.

Methods and analysis The Pediatric Adenotonsillectomy Trial for Snoring (PATS) is a single-blinded, multi-center randomized controlled trial designed to evaluate the effect of adenotonsillectomy in treating mild obstructive sleep-disordered breathing. Four hundred sixty eligible children, aged 3.0 to 12.9 years old, will be randomized to either early adenotonsillectomy (AT) or to watchful waiting with supportive care (WWSC) with 1:1 ratio. The study's co-primary endpoints are: a) Behavioral Rating Inventory of Executive Function [BRIEF] Global Composite Score [GEC]; and b) the Go-No-Go (GNG) continuous performance test. A mixed effects model will be used to compare changes in the BRIEF GEC score and GNG score at 6 and 12 months from baseline between the AT arm and the WWSC arm.

Ethics and dissemination The study protocol was approved by the institutional review board at Children's Hospital of Philadelphia (CHOP) on October 3rd, 2014 (14-011214). The approval of CHOP as the central IRB of record was granted on February 29, 2016. The results will be published in peer-reviewed journals and presented at academic conferences. The data collected

from the PATS study will be deposited in a repository (National Sleep Research Resource; sleepdata.org) after completion of the study to maximize use by the scientific community.

Registration: NCT02562040 Pediatric Adenotonsillectomy Trial for Snoring (PATS) www.clinicaltrials.gov

Key Words: snoring, pediatrics, sleep apnea, sleep-disordered breathing, clinical trial, asthma, health care utilization.

Article Summary

Strengths and limitations of this study

- Evaluation of the benefit and adverse effects of surgical intervention versus watchful waiting, including assessment of associated healthcare utilization.
- Adoption of co-primary endpoints that includes parent-reported and objectively collected neurocognitive measures.
- Collection of a large variety of data from multiple sources (child, caregiver, teacher, and neighborhood geocode) and across multiple domains (neurobehavior, polysomnography, actigraphy, symptoms, quality of life, anthropometry, blood pressure, health care utilization, tobacco exposure, immunoglobulin titers).
- Supported by an Informatics and Data Management Core that develops and integrates cutting-edge, open-source web development tools and dynamic research data.
- Double-blinding was not feasible for a surgical trial in children.

INTRODUCTION

Obstructed sleep-disordered breathing (oSDB) is common in the pediatric population and is associated with significant morbidity[1]. Adenotonsillectomy(AT), the second most common surgery performed under general anesthesia in children (more than 289,000 times per year in the US)[2], is generally considered the first line treatment for oSDB in otherwise healthy children ages 2-18 with adenotonsillar hypertrophy[3]. This procedure is often performed on children with symptoms of oSBD without polysomnographic evidence of frequent apneas or hypopneas[4]. The single randomized controlled study examining outcomes of pediatric AT for obstructive sleep apnea syndrome (OSA) (Childhood Adenotonsillectomy Trial, CHAT) included only children with polysomnographically-documented obstructive sleep apnea[5]. The CHAT study found that AT compared to watchful waiting resulted in improved behavior, quality of life, OSA symptoms and polysomnographic parameters, but did not lead to significant improvement in objective measures of attention or executive function. Of note, almost half of the children not undergoing AT had polysomnographic resolution of the OSA over a 7-month period[6].

While screening children for inclusion in the CHAT study it became apparent that almost half of symptomatic children considered to be surgical candidates for AT had what are often considered less severe forms of oSDB including snoring, flow limitation or mild oOSA (obstructive Apnea Hypopnea Index [oAHI]<3). These entities could be grouped together and classified as mild sleep-disordered breathing (mild oSDB). Evidence to date has shown little correlation between severity of oSBD and neurocognitive morbidity[5 7 8]. Moreover, several studies have also demonstrated that mild oSDB is associated with more severe neurobehavioral impairment that is more easily reversed with appropriate intervention[7 8]. Rigorously controlled

data are not available on the benefits of AT for mild oSDB, or for treating younger children, who may be most sensitive to the effects of sleep problems due to developmental plasticity. Lack of data has led to huge geographical variability in the USA with regards to the management of mild oSDB, with the rate of AT per 10,000 children varying from 28.9 in the West to 125.1 in the South[9]. Unnecessary surgery may expose children to risk, and the health care system to considerable costs. Conversely, withholding effective treatment from children could result in substantial short and long-term health burdens to the child, their family, and society. Effective and timely treatment could also potentially reduce health care costs associated with symptoms and co-morbidities that are exacerbated by the presence of mild oSDB. Understanding the role of treatment for mild oSDB is of especial importance given the increased prevalence of SDB among vulnerable groups of children, such as racial minorities[10]. Filling these gaps in knowledge is critical to inform clinical guidelines, decision-making, and appropriate utilization of interventions in populations most likely to benefit.

The goal of the Pediatric Adenotonsillectomy Trial for Snoring (PATS; '*The impact of treatment of mild sleep-disordered breathing in children's health'*) is to provide high quality evidence regarding the effects of surgical intervention versus watchful waiting (observation) on a group of healthy children with nocturnal obstructive symptoms whose polysomnograms demonstrate mild oSDB. This study was specifically designed to evaluate the effectiveness of AT as well as associated healthcare utilization (HCU) in children with mild oSDB. In this article, we present the PATS protocol (version 19; February 19, 2019) and describe the special challenges in designing a RCT of a surgical intervention in young children including selecting appropriate outcomes, determining approaches for collection of HCU data across geographically diverse US sites, and optimizing data collection in studies of young children.

METHODS AND ANALYSIS

Study Overview

PATS is a multi-center, randomized, single-blinded 12-month intervention study that compares the impact of AT on measures of behavior, quality of life, sleep-related symptoms, polysomnographic findings, and HCU in children with mild oSDB (Figure 1). Children with symptoms of mild oSDB are recruited from each site's otolaryngology, sleep, pulmonary, and/or general pediatric clinics. At baseline, participants undergo neurobehavioral testing and polysomnography (PSG) and assessment of patient-reported outcomes (sleepiness, quality of life, sleep quality), anthropometry, and blood pressure. All measures are repeated at 6 and 12 months, except that the PSG is only repeated at 12 months. In addition to baseline, 6-month, and 12-month visits, participants receive monthly telephone calls to maximize retention and to collect interim data on symptoms and HCU. The study started enrollment since June 2016. As of August 26, 2019, 344 children have been randomized. The reporting of the PATS protocol follows the SPIRIT reporting guidelines[11].

Study Aims and Endpoints

The primary objectives are to determine the effect of early AT (eAT) versus Watchful Waiting with Supportive Care (WWSC) on a co-primary outcome: executive function assessed by a parent behavior rating (Behavior Rating Inventory of Executive Function Global Executive Composite, second edition or preschool version; BRIEF2/P GEC[12 13]), and children's sustained attention as assessed by signal detection parameter (d-prime) for performance on the Continuous Performance Test (CPT) from the Go-No-Go task[14].

The secondary objectives are: 1) to determine the effect of eAT versus WWSC on oSDB symptoms and quality of life. We also will track and compare group changes in HCU occurring within each site's medical system and externally, as well as filled prescriptions. Exploratory analyses propose assessment of changes in anthropometry and blood pressure; 2) identification of factors that moderate the response to AT, including age, socioeconomic status (SES), race, asthma/atopy, second-hand smoke exposure, short sleep duration and family functioning competencies. A detailed list of these variables is provided in Table 1.

Study Organization

The study is supported by a Data Coordination Center (DCC)/Sleep Reading Center (Brigham and Women's Hospital; Boston, MA), charged with development of the study's statistical design and monitoring plans, construction and management of the study database and study materials, and generation of statistical reports to investigators and the PATS Data and Safety Monitoring Board (DSMB). The Sleep Reading Center is charged with centralized PSG scoring and generation of standardized PSG variables. A surgical quality assurance core is based at the University of Michigan, Ann Arbor, MI. A neuropsychology core is provided by psychologists at two sites (Children's Hospital of Philadelphia PA and Nationwide Children's Hospital Research Institute, Columbus, OH).

The study is also supported by a Clinical Coordinating Center (CCC), Children's Hospital of Philadelphia, PA, charged with overseeing the activities at the clinical sites, regulatory approvals, and providing clinical expertise. Clinical sites are each headed by a sleep medicine physician or an otolaryngologist and, together with their local research team (study coordinators, trained psychometricians, sleep laboratory staff) are responsible for recruitment and follow-up of participants. Initially, 5 clinical sites (Children's Hospital of Philadelphia, PA;

Cincinnati Children's Medical Center, OH; Rainbow Babies & Children's Hospital at University Hospitals – Cleveland Medical Center, OH; University of Michigan Health System, Ann Arbor, MI, University of Texas Southwestern Medical Center, Dallas, TX) were identified to participate in the study. In July 2018, two new sites (Children's Hospital, Boston, MA; Children's Hospital of the King's Daughters, Norfolk, VA) were added to improve subject accrual. In June 2019, Boston Children's Hospital was closed to accrual upon DSMB's recommendation due to its slow accrual, resulting in 6 recruitment sites.

Study governance is through a Steering Committee with representation from each participating site, key quality control cores, and National Health Lung Blood Institute (NHLBI) program staff. An Executive Committee, consisting of the Study Chair, the DCC Directors, CCC Director, and the NHLBI project officer, who regularly meets by telephone to address emerging issues. Sub-committees are organized to address the multiple quality control and monitoring needs of the study: Surgical Quality Control, Neuropsychology Quality Control, Polysomnography Quality, Recruitment and Operations, and Publications and Presentations. An independent Data and Safety Monitoring Board (DSMB), with expertise in pediatric ethics, surgery, sleep apnea, clinical trials, and biostatistics, appointed by and reporting directly to the NHLBI, reviews quarterly reports and meets semi-annually to assess the emerging data and make recommendations. A board-certified pediatric sleep medicine physician is continuously available as an independent medical monitor (MM).

Sample Population and Enrollment

This study recruits children with symptoms of mild oSDB and their caregivers. The inclusion criteria are: 1) Ages 3.0 to 12.9 years at the time of screening; 2) Diagnosis of mild oSDB

defined as: a. Parent report of habitual snoring that occurs most of the night on at least 3 nights per week, and has been present for at least 3 months (on average occurring > 3 nights per week or more than one-half the sleep time) and b. Obstructive apnea index < 1/hour and obstructive apnea-hypopnea index <3/hour and no oxyhemoglobin desaturation < 90% in conjunction with obstructive events, confirmed on nocturnal, laboratory-based PSG; 3) Tonsillar hypertrophy ≥ 2 based on a standardized scale of 0-4; 4) Determined to be a candidate for AT by ENT evaluation ; and 5) Primary indication for AT is nocturnal obstructive symptoms. As in all RCTs, equipoise about randomization in PATS is required on the part of participants, their families, and their clinicians (ENT surgeons).

The exclusion criteria are: 1) Previous tonsillectomy; 2) Recurrent tonsillitis that merits prompt AT per the American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guidelines [3]; 3) Severe obesity (body mass index; BMI z-score ≥ 3); 4) Severe chronic health conditions that might hamper participation or confound key variables under study; 5) Current use of psychotropic medication (other than medications for Attention-Deficit Hyperactivity Disorder (ADHD), hypnotics, antihypertensives or growth hormone; 6) History of severe developmental disability or ABAS (Adaptive Behavioral Assessment System) score < 60; 7) Parent/guardian unable to accompany the child on the night of the PSG; 8) Family planning to move out of the area within the year; 9) Family does not speak English or Spanish well enough to complete the behavioral and performance measures; 10) Child in foster care.

Study Interventions

Depending on the randomized treatment assignment, participants are assigned to either WWSC or eAT. Within 4 weeks of randomization, participants randomized to the eAT arm undergo

surgery under general anesthesia, as part of routine clinical care. Surgery is performed by board-certified otolaryngologists with or without the assistance of resident physicians in accredited otolaryngology training programs. Prior to the surgical procedure, tonsillar size is graded using a standardized scale of 0-4[15]. Extent of adenoid tissue is graded as mild (0- 33%), moderate (34-66%) or severe (67-100%) obstruction of the posterior choanae intra-operatively in subjects undergoing AT. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue are performed by cold dissection, monopolar electrocautery or any other recognized surgical technique.

Regardless of the treatment assignment, all participants receive sleep and healthy lifestyle education. Standardized materials recommended by the National Institutes of Health and pediatric professional sleep societies are used to reinforce optimal sleep health and educational play is encouraged by providing take-home materials addressing sleep health. Other supportive care is provided at initial evaluation and as needed throughout the course of the trial. For example, participants identified as having suboptimal asthma or nasal allergy control will be referred to their primary care physician for management and further treatment of these problems.

After 12 months, children who did not undergo AT who have a 12-month PSG showing concerns for oSDB or whose parent reports ongoing symptoms/concerns are referred back to ENT for further clinical management (such as AT, if still indicated) as per standard clinical care.

Blinding

As in CHAT, the use of a surgical intervention prevents blinding of the child, parent, and certain staff members. PATS adopts a similar approach where the principal investigators at each site (other than sites at which the PI is a surgeon), psychometricians, and study coordinators who

directly collect primary outcomes are blinded to study treatment. In addition, all DCC and CCC staff except for those responsible for statistical analyses, data management, and AE adjudication and communication are blinded. The responsibilities of blinded and unblinded staff at each site has been clearly delineated and a structured format for communication was established to minimize the impact of the unblinding on study outcomes and study progress.

Neuro-behavioral Testing

To ensure reliable collection of neurobehavioral test data, much attention was directed at developing a rigorous protocol for training research assistants to properly administer the tests. Initial training was provided by in-person review and demonstration of procedures. Examiners later reviewed administration procedures, practiced the assessments with other team members, and made video recordings of an assessment conducted with a child volunteer. To ensure fidelity of test administration, the videos were reviewed by one of the two psychologists in the Neurobehavioral Core, with feedback provided and additional assessments required if procedures did not meet specific competency criteria. The challenge in testing young children, some of whom had limited attention spans and difficulty in following through on test instructions, was addressed by selecting engaging tests that were "hands-on" and could be easily understood by children as young as 3 years. Testing procedures included defined opportunities for children to practice, with repetition of instructions. Recognizing that despite these procedures, there would still be some variation in engaging children, protocols were developed to allow the examiners to document behaviors that may have contributed to test performance, such as inattention or off-task behaviors.

Informatics and Data Management Core (IDMC)

PATS is supported by an innovative Informatics and Data Management Core (IDMC) that develops and integrates cutting-edge, open-source web development tools and dynamic research data, providing robust and highly interactive tools for multicenter studies, clinical trials and data repositories. These tools are developed and updated on a weekly basis using a continuous deployment methodology based on the agile software development framework. The Core provides thorough documentation of the software and the deployment architecture in the form of online version-controlled documentation, and web-based video tutorials. Electronic data entry is supported by the software program *Slice* (https://sliceable.org), which excels at dynamic in-application reporting and provides researchers, individual clinical sites, the DSMB and the sponsor a live snapshot of the current state of the database. *Slice* also provides robust project management tools, including the ability to easily create and track participant/study schedules. Data interoperability is handled by the Spout JavaScript Objective Notation (JSON) (https://www.json.org/) data dictionary framework to modularize data definitions into small, maintainable versioned data element descriptors. Finally, the IDMC promotes data liberation, enabling researchers to export all data they have entered at any point in a useable format that can be imported into a new system of their choice.

Health care utilization (HCU) and electronic medical record (EMR) surveillance

The study addressed challenges in collecting consistent and complete HCU from multiple, diverse medical centers that utilize different EMRs and from families who may utilize health care services outside of PATS clinical sites. To comprehensively identify episodes of HCU, a surveillance approach was developed that includes the following: 1) a semi-structured interview undertaken on a monthly basis with caregivers when information is gathered regarding any HCU 'billed and filled' (that is, any healthcare encounter and any filled

prescription; 2) the local EMR is queried approximately quarterly in order to ensure that no internal HCU (encounters or prescriptions within the local medical system) was missed during caregiver interviews; and 3) attempts are made to receive medical reports based on any caregiver reports of external HCU (encounters or prescriptions outside of the local medical system that are not visible in the local EMR). Prior to study start, meta-data for common pediatric HCU events were identified to develop a standardized HCU data dictionary which was supplied to each participating site. A medical record analyst from each site was asked to develop an electronic query designed to pull appropriate data at planned intervals. HCU data are entered into a cumulative electronic log by the unblinded coordinator from each site, encompassing hospitalizations (reason, location, and number of days), unscheduled and scheduled outpatient visits, and filled medication prescriptions. Given the marked variability in EMR and resources across sites, procedures for undertaking the quarterly EMR queries vary: some sites have an analyst working directly with project staff to request a batch of data whereas other sites train coordinators to query their EMR using script developed by an analyst. The quarterly EMR queries each cover a period of four months such that there is always overlap across queries, as there can be delays in data being populated in the EMR. Completed logs (de-identified apart from the inclusion of dates) are transferred to the DCC via an encrypted data transfer method; source data are maintained on a secure server at each site.

Statistical Considerations

A total of 460 children are randomized to one of the two treatment arms in a 1:1 ratio. Factors identified to possibly influence treatment response include child's age (reflecting developmental differences in neuro-behavior and potential sensitivity to oSDB), weight status (a co-morbidity that may portend less effective surgical responses) and race (based on prior data

indicating suboptimal surgical response of African American compared to white children)[5]. Therefore, randomization is stratified by the following factors within site: age (< 5 years vs > 5 years); overweight status (body mass index [BMI] >85th percentile); and race (African American vs other). Stratification provides greater assurance that the comparison groups will be similar with respect to these variables. However, given the overall sample size of 460 and the relatively large number of strata (8 strata within each of the 7 sites), the expected total number of subjects within each stratum is too small (about 8) to use standard randomization approaches such as permuted blocks. To ensure that treatment arms are balanced with respect to these factors as well as for the number of subjects in each group, we use a dynamic randomization method, Pocock and Simon's minimization method [16]. Specifically, for each eligible participant, based on the value of his/her stratification factors, the participant will have a 30% chance to be allocated randomly to one of the two treatment arms, and a 70% chance to be allocated to the arm that minimizes the differences in number of participants across two treatment arms within each stratum deterministically. We have implemented this randomization algorithm in our Data Management System (Slice).

Based on the experience in the CHAT study, we assume a drop-out rate of 15% at 6 months, and an additional 5% attrition at 12 months, resulting in 390 and 368 evaluable subjects at 6 and 12 months, respectively. In designing this study, we chose the sample size so that the study will have ample power for testing the primary and key secondary hypotheses and adequate power to detect moderate to large moderation effects.

In CHAT, greater improvements in the BRIEF score were observed in the eAT vs WWSC arm but we could not rule out the possibility that these improvements were influenced by parental expectations. Therefore, in PATS, we elected a co-primary outcome that included

one objective neurocognitive measure (the GNG d-prime score for sustained attention) and one composite behavioral outcome (the BRIEF2/P GEC score). To maintain a study-wise significance level of 5% for analysis of co-primary endpoints, we use a sequentially rejective method, the Holm's method, which has been shown to be uniformly more powerful that the Bonferroni procedure. In the case of two tests using an overall alpha of 0.05, the comparison with the largest difference will be tested at the 0.025 level. If it is rejected, the comparison with the second difference will be tested at the 0.05 level. For the BRIEF score change from baseline to 12 months, we used prior CHAT data and assumed a relatively large 3.7 points difference in change scores between the two arms, a 11.5 points standard deviation at baseline and a correlation between the baseline and the follow-up measurements of 0.73. For the GNG change score, we assumed a smaller 0.33 difference in d-prime score between the two arms, a baseline standard deviation of 0.77, and a correlation between baseline and follow-up measurements of 0.48[14]. Using these estimates and methods described in Hedeker et al.[17] for sample size estimation for longitudinal designs with attrition, our sample size with the assumed attrition rate has 98% power to detect a difference of 3.7 points in the BRIEF 2/P GEC change score and 98% power to detect a difference of 0.33 points in the GNG change score between treatment groups at a significance level of 2.5% and 5%, respectively.

Primary analyses will follow the "intention-to-treat" principle and use a mixed effects model relating outcomes and treatment group indicators. Time (0, 6, and 12 months) will be modeled as a categorical variable to allow separate comparisons of intervention effect at 6 and 12 months. Missing data will be handled through multiple imputation[18] or inverse probability weighting[19]. Continuous secondary outcomes will be analyzed in the similar fashion as the primary outcome. For endpoints related to HCU, we will consider models that account for

potential data dispersion and possible preponderance of zeros (e.g., zero-inflated negative binomial models). Statistical tests of treatment by covariate interaction will be performed to assess whether treatment effect varies by age, baseline weight, atopy/asthma status, second-hand smoke, socioeconomic status, family functioning, or race.

Safety and Data Monitoring

The study is monitored routinely for issues of data quality, study conduct (including recruitment and follow-up rates), data quality, and adverse events. Of particular concern are attrition and cross-over rates which, if excessive, could jeopardize the integrity of the study. A special category of event, denoted as "treatment failure" was utilized in the CHAT study and is also used in PATS. Treatment failures are identified using pre-specified thresholds for defining changes in behavior or health likely attributable to persistent mild oSDB, adjudicated by an independent medical monitor. Adverse event surveillance, adjudication, and reporting follows the requirements of NHLBI and the central reliant IRB at CHOP, as well as any site-specific IRB requirements. Quarterly reports addressing these issues of study conduct, data quality, adverse events and treatment failures are provided to the Steering Committee, the DSMB and NHLBI. Given that the patient population consists of children who are otherwise healthy, with mild oSDB, and that the intervention is considered a standard clinical intervention, we do not anticipate that the interim analysis will yield efficacy data compelling enough to require early termination. Therefore, we will monitor the BRIEF2/P GEC score and GNG score, the co-primary outcomes, in planned interim analyses of efficacy. We plan to perform one interim analysis after half of the study population has completed their 12-month evaluations. Based on our recruitment projections, most of the accrual will be complete at this time and therefore early stopping may not be relevant. To create a formal framework for assessment of interim results,

the Haybittle-Peto boundary will be used [20]. That is, interim results for comparisons of the BRIEF2/P score and GNG score between treatment groups will be considered sufficient to consider early termination only if at least one of the between group differences are statistically significant using a family-wide significance level of 0.001. The Haybittle-Peto stopping rule allows the final analysis to be evaluated at a 5% level of significance [20 21].

Patient and Public Involvement Statement

The design of this study is informed by the experience of participants and their families in the CHAT study, where study staff heard of interest in understanding the impact of snoring on quality of life and cognition. The teachers of the participating children provided standardized neurobehavioral assessments during the course of the study. The conduct of the study is overseen by the DSMB that includes representatives from the National Institutes of Health. We plan to use data from this study to disseminate information directly to patients through educational modules, blogs and an on-line forum available in a sleep apnea patient portal (MyApnea.Org)that has enrolled over 17,000 patients and their family members to learn more about sleep apnea and ongoing sleep apnea research.

ETHICS and DISSEMINATION

The potential consequences of deferring surgery and treating oSDB conservatively are unclear, and provide the rationale for this randomized controlled trial. There is great physician and geographical differences regarding whether or not oSDB is treated surgically. In many centers, children with a normal PSG do not undergo AT and in other centers, children who snore do not undergo PSG (precluding distinction of OSA from oSDB). All options, including refusal to be in the study in order to obtain more immediate treatment, as well as potential risks of surgery, will

be discussed with the participants and their families. At the end of the trial, participants will have a final PSG, and children with persistent symptoms of SDB or new abnormalities on PSG will be referred for clinical management.

The study protocol, IRB# 14-011214, was approved by the institutional review board at Children's Hospital of Philadelphia (CHOP) on October 3rd, 2014. Following NIH policies, it was decided that the CHOP IRB would be the study's single central IRB. Participating sites provided reliance agreements allowing the CHOP IRB to act as the IRB of record for their institutions. The relying institutions remain responsible for ensuring compliance with the CHOP IRB's determinations and with the Terms of its Office of Human Research Protections – approved Federal Wide Assurance. The approval of CHOP as the central IRB of record was granted on February 29, 2016. Each clinical center is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its IRB. Informed consent (signed and dated by the participant's parent/guardian) must be obtained prior to initiation of any study related activity.

Proposed protocol changes are presented to the Steering Committee 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 CCC and DCC will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol. Substantive changes to the protocol require approval from the DSMB before implementation.

To maintain patient confidentiality, participants are identified to the DCC only by patient identification numbers and no personal information will be transmitted to the DCC. Furthermore,

data for reports and publications will be provided in aggregate or blinded form without the identification of individual patients. At the clinical sites and participating centers, all data will be: 1) kept in confidential locked files; 2) identified by participant identification number only; 3) kept separately from identifying information used for participant tracking and follow-up contacts.

The results will be published in peer-reviewed journals and presented at academic conferences, as well as directly to patients through a web portal MyApnear.org. The data collected from the PATS study will be deposited in a repository (National Sleep Research Resource; sleepdata.org) after completion of the study to maximize use by the scientific community.

DISCUSSION

Mild oSDB is of great clinical and public health relevance given its high prevalence and potential impacts to health and well-being of children, their families, and the health care system. A paucity of data from randomized clinical trials has led to fundamental questions regarding the role of AT in children with mild oSDB, contributing to large geographical variations in care and potential for surgery to be both over- and under-utilized. PATS was designed to resolve uncertainties on management approaches for pediatric mild oSDB by addressing several critical issues: a) assess outcomes of importance to children and their families - in particular, the patient-reported outcomes of behavior, quality of life, and sleep disturbances; b) examine differences in treatment responses among children who are at increased risk for mild oSDB, such as pre-school children, minorities, and children with asthma or obesity; c) evaluate HCU as an under-studied outcome in this condition; and d) assess moderating influences of second-hand smoke, insufficient or irregular sleep, socioeconomic status (SES) and family functioning. Meeting the

study goals requires collection of a large variety of data from multiple sources (child, caregiver, teacher, and neighborhood geocode) and across multiple domains (neurobehavior, polysomnography, actigraphy, symptoms, quality of life, anthropometry, blood pressure, health care utilization, cotinine, immunoglobulin titers).

Several challenges present in the design of PATS. 1) The targeted study population include children aged from 3.0 to 12.9 years at the time of screening. In accord with the rapid development of children in this age range, age-specific forms are available for both the BRIEF and GNG tests. Therefore, the tests given at each visit are age-dependent. During the 12-month follow-up period, children may move from one age group to another age group, resulting in different age-specific tests used at baseline and at the 12-month follow-up. However, the test scores are normalized to each age category making them comparable across different groups. Furthermore, age has been chosen as a stratification factor to ensure balance across treatment arms within each age category. Effect modification by age will also be examined as a pre-specified subgroup analysis. 2) Recall bias may present, especially when reporting behavior problems; parents may differ in their vigilance in monitoring their children's behavior problems or adverse events in general and willingness to discuss these issues with the study coordinator, and such differences may not be balanced by treatment arm. When analyzing safety data, sensitivity analyses may be needed to quantify the potential effect of such bias. 3) Double-blinding is not possible in a study of surgical treatment in children. Parents and children cannot be feasibly blinded to surgery. The use of a caregiver-reported outcome is of concern in this setting as responses may reflect treatment expectations. We attempted to address this concern by including an objective test (GNG) as a co-primary outcome as well as collecting comparable behavioral data from the child's teachers, who may be unaware of treatment. To minimize bias

due to unblinded staff, we established structured communication protocols between blinded and unblinded personnel at each site. Nonetheless, unblinding may occur especially considering the study's frequent contact points between parents and study personnel (three visits and monthly phone calls). Every effort is made to prevent unblinding and any unblinding episodes are documented to facilitate the interpretation of study findings. 4) As in any clinical trial, cross-over and loss to follow-up will be inevitable despite attempts at best practice. While cross-over does not threaten the validity of the intent-to-treat primary analysis, it may dilute the treatment effect and reduce the study power. The rate of cross-over is closely monitored and its effect on study power will be assessed. 5) HCU data are from diverse academic health care centers in the U.S. where costs are difficult to directly assess due to the discrepancies between costs and charges. Therefore, our analyses will quantify key HCU events (e.g. hospitalizations, clinic visits, medications, etc), which will provide a proxy for costs.

In summary, PATS will provide evidence on whether children with mild oSDB benefit from surgery, by randomizing children to the two most common managements: adenotonsillectomy or observation. The findings will have key implications for disease management, including the need for pre-operative PSGs to distinguish oSDB from obstructive sleep apnea, the potential to reduce practice and geographic variability in the management of oSDB, and the understanding of response to surgery in African American children and in lower socio-economic status families, in order to optimize their management and reduce health disparities. Moreover, the design of PATS provides a model for conducting a surgical trial in children across a large age range studied with both caregiver reported and objectively measured outcomes, while also assessing a wide range of other outcomes such as HCU and potential effect modification by several host and environmental factors. Salient statistical considerations include

plans for analysis of a co-primary outcome without excessive loss of power; use of a dynamic randomization method to address multiple strata of interest in the context of a modest sample size; analysis of complementary caregiver and teacher reports; and interim safety analyses that minimally impact study power.

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AUTHOR CONTRIBUTIONS

All authors drafted and revised sections of the study protocol according to their expertise. First draft of the manuscript: RW and SR. All authors critically reviewed and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

Dr. Bakker is a full-time employee of Philips, a company that focuses on sleep and respiratory care. Dr. Bakker also has a part-time appointment at Brigham and Women's Hospital. Dr.

Bakker's interests were reviewed and are managed by BWH and Partners HealthCare in accordance with their conflict of interest policies. Dr. Chervin reports service on the boards of the American Academy of Sleep Medicine, Associated Professional Sleep Societies, American Board of Sleep Medicine, American Academy of Sleep Medicine Foundation, International Pediatric Sleep Association, and the not-for-profit Sweet Dreamzzz. He serves as an author and editor for UpToDate. Dr. Fauziya received research funding from Jazz pharmaceuticals and is a consultant for Biogen (Spinraza); none is relevant to this manuscript. Dr. Rosen is a member of American Academy of Medicine and the American Academic of Sleep Medicine Foundation Board of Directors. She has no financial disclosure that is relevant to this manuscript. Dr. Ross reports non-financial support from BI, grants and non-financial support from TEVA, non-financial support from GSK, non-financial support from Merck, grants from Flamel, grants from Jazz, and grants from Astra Zeneca, outside the submitted work. Dr. Redline received institutional grants from Jazz Pharmaceuticals and consulting fees from Jazz Pharmaceuticals and Respicardia. The other authors have no financial conflicts of interest.

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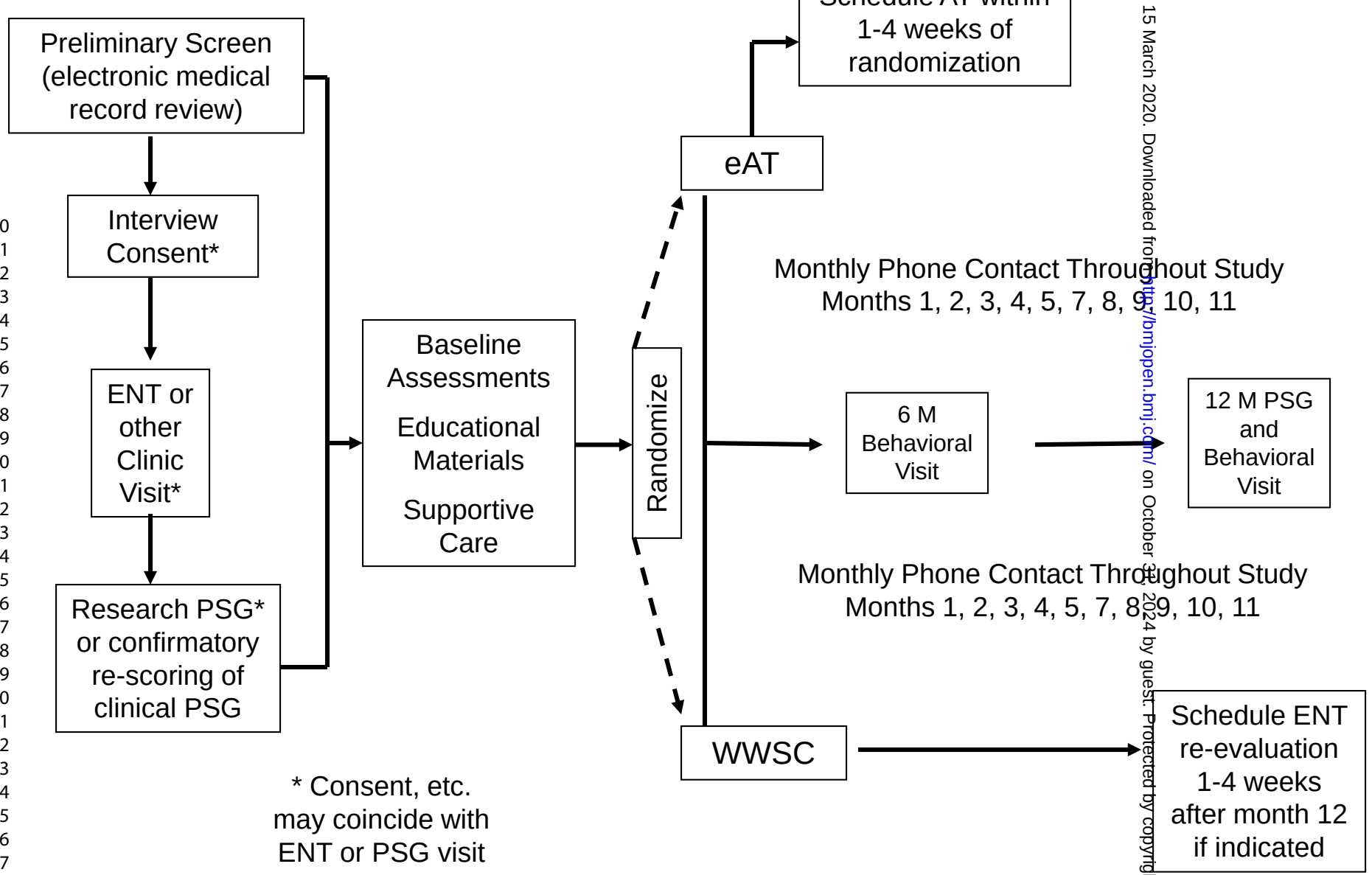
Table 1. Primary, secondary endpoints, pre-specified candidate moderators.

Primary endpoints	BRIEF2/P Global Executive Composite Score[12 13]
	GNG sustained attention d-prime parameter[14]
Secondary endpoints	
Objective performance testing	GNG inhibitory control d-prime[14]
	Fine motor coordination: NIH-Toolbox 9-Hole Pegboard Dexterity Test
Behavioral scale	Executive function: BRIEF 2/P meta-cognition and emotional regulation summary scores and subscales for parent and teacher reports
	Behavior: Child Behavior Checklist (CBCL)[22] summary scale and subscores, parent and teacher ratings
	Attention: Conners 3 Short Form (caregiver and teacher versions) Global Index T score and subscales[23]
SDB symptoms	Pediatric Sleep Questionnaire: Sleep-Related Breathing Disorder (PSQ-SRBD) Scale total score[24]
	Sleepiness: Epworth Sleepiness Scale modified for children summary score and PSQ-SRBD sleepiness scale[25]
	Snoring: The Patch Snoring Sensor
Quality of life	Generic: Pediatric Quality of Life Inventory (PedsQL) total score and subscores[26]
	Disease specific: OSAS-18 total score
Physical exam	Measurements of weight; height; body mass index (BMI); waist, hip, neck circumferences
	Systolic, diastolic and mean blood pressure levels
Health Care Utilization	Medications, health care visits (scheduled, unscheduled), ascertained from caregiver reports, EMR surveillance, billing and pharmacy records, hospitalizations
Potential Effect Modifiers	
	Demographics: race, SES (parent education, family income, financial stress rating scale, geocode data on neighborhood characteristics)

	Sleep duration and efficiency: objective assessment by 7-day wrist actigraphy
	Asthma/atopy: IgE, International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, review of EMR and parent interview (using NHLBI asthma definitions based on a history of asthma and use of asthma medications)
	Second-hand smoke exposure: urinary cotinine
	Family functioning cluster: family functioning (Family Assessment Device, short form); parenting style (Parenting Style Questionnaire); parent perception of stress (Parenting Stress Index 4th ED., short form); medical literacy (Rapid Estimate of Adult Literacy in Medicine, Revised); discrimination (Experiences of Discrimination)

Figure 1. An Overview of Study Design.

Fig. 1: Study design



Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	23

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8,9,17,18
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5,6
Objectives	#7	Specific objectives or hypotheses	7,8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7,14,15
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	8,9

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9,10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14,15
Recruitment	#15	Strategies for achieving adequate participant enrolment	15

		to reach target sample size	
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11,12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference	12,13,14

		to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16,17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17,18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17,18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	17,18

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19,20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23,24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing	20

		arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	S1-17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Pediatric Adenotonsillectomy Trial for Snoring (PATS): Protocol for a Randomized Control Trial to Evaluate the Effect of Adenotonsillectomy in Treating Mild Obstructive Sleep-Disordered Breathing

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine
Keywords:	snoring, pediatrics, sleep apnea, sleep-disordered breathing, clinical trial, Asthma < THORACIC MEDICINE

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Pediatric Adenotonsillectomy Trial for Snoring (PATS): Protocol for a Randomized Control Trial to Evaluate the Effect of Adenotonsillectomy in Treating Mild Obstructive Sleep-Disordered Breathing

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Abstract

Introduction Mild obstructive sleep-disordered breathing (oSDB), characterized by habitual snoring without frequent apneas and hypopneas on polysomnography, is prevalent in children, and commonly treated with adenotonsillectomy (AT). However, the absence of high-level evidence addressing the role of AT in improving health and behavioral outcomes has contributed to significant geographical variations in care and potential for surgery to be both over- and under-utilized.

Methods and analysis The Pediatric Adenotonsillectomy Trial for Snoring (PATS) is a single-blinded, multi-center randomized controlled trial designed to evaluate the effect of adenotonsillectomy in treating mild obstructive sleep-disordered breathing. Four hundred sixty eligible children, aged 3.0 to 12.9 years old, will be randomized to either early adenotonsillectomy (AT) or to watchful waiting with supportive care (WWSC) with 1:1 ratio. The study's co-primary endpoints are: a) Change from baseline in executive behavior relating to self-regulation and organization skills as measured by the Behavioral Rating Inventory of Executive Function [BRIEF] Global Composite Score [GEC]; and b) Change from baseline in vigilance as measured on the Go-No-Go (GNG) signal detection parameter (d-prime). A mixed effects model will be used to compare changes in the BRIEF GEC score and GNG score at 6 and 12 months from baseline between the AT arm and the WWSC arm.

Ethics and dissemination The study protocol was approved by the institutional review board at Children's Hospital of Philadelphia (CHOP) on October 3rd, 2014 (14-011214). The approval of CHOP as the central IRB of record was granted on February 29, 2016. The results will be

published in peer-reviewed journals and presented at academic conferences. The data collected from the PATS study will be deposited in a repository (National Sleep Research Resource; sleepdata.org) after completion of the study to maximize use by the scientific community.

Registration: NCT02562040 Pediatric Adenotonsillectomy Trial for Snoring (PATS) www.clinicaltrials.gov

Key Words: snoring, pediatrics, sleep apnea, sleep-disordered breathing, clinical trial, asthma, health care utilization.

Article Summary

Strengths and limitations of this study

- Evaluation of the benefit and adverse effects of surgical intervention versus watchful waiting, including assessment of associated healthcare utilization.
- Adoption of co-primary endpoints that include parent-reported and objectively collected performance-based neurocognitive measures.
- Collection of a large variety of data from multiple sources (child, caregiver, teacher, and neighborhood geocode) and across multiple domains (neurobehavior, polysomnography, actigraphy, symptoms, quality of life, anthropometry, blood pressure, health care utilization, tobacco exposure, immunoglobulin titers).
- Supported by an Informatics and Data Management Core that develops and integrates cutting-edge, open-source web development tools and dynamic research data.
- Double-blinding was not feasible for a surgical trial in children.

INTRODUCTION

Obstructed sleep-disordered breathing (oSDB) is common in the pediatric population and is associated with significant morbidity[1]. Adenotonsillectomy(AT), the second most common surgery performed under general anesthesia in children (more than 289,000 times per year in the US)[2], is generally considered the first line treatment for oSDB in otherwise healthy children aged 2-18 with adenotonsillar hypertrophy[3]. This procedure is often performed on children with symptoms of oSBD without polysomnographic evidence of frequent apneas or hypopneas[4]. The single randomized controlled study examining outcomes of pediatric AT for obstructive sleep apnea syndrome (OSA) (Childhood Adenotonsillectomy Trial, CHAT) included only children with polysomnographically-documented obstructive sleep apnea[5]. The CHAT study found that AT compared to watchful waiting resulted in improved behavior, quality of life, OSA symptoms and polysomnographic parameters, but did not lead to significant improvement in objective measures of attention or executive function. Of note, almost half of the children not undergoing AT had polysomnographic resolution of the OSA over a 7-month period[6].

While screening children for inclusion in the CHAT study it became apparent that almost half of symptomatic children considered to be surgical candidates for AT had what are often considered less severe forms of oSDB including snoring, flow limitation or mild oOSA (obstructive Apnea Hypopnea Index [oAHI]<3)[5]. These entities could be grouped together and classified as mild sleep-disordered breathing (mild oSDB). Evidence to date has shown little correlation between severity of oSBD and neurocognitive morbidity[5 7 8]. However, several studies have demonstrated that mild oSDB is associated with more severe neurobehavioral impairment that is more easily reversed with appropriate intervention[7 8]. Rigorously controlled

data are not available on the benefits of AT for mild oSDB, or for treating younger children, who may be most sensitive to the effects of sleep problems due to developmental plasticity. Lack of data has led to huge geographical variability in the USA with regards to the management of mild oSDB, with the rate of AT per 10,000 children varying from 28.9 in the West to 125.1 in the South[9]. Unnecessary surgery may expose children to risk, and the health care system to considerable costs. Conversely, withholding effective treatment from children could result in substantial short and long-term health burdens to the child, their family, and society. Effective and timely treatment could also potentially reduce health care costs associated with symptoms and co-morbidities that are exacerbated by the presence of mild oSDB. Understanding the role of treatment for mild oSDB is of especial importance given the increased prevalence of SDB among vulnerable groups of children, such as racial minorities[10]. Filling these gaps in knowledge is critical to inform clinical guidelines, decision-making, and appropriate utilization of interventions in populations most likely to benefit.

The goal of the Pediatric Adenotonsillectomy Trial for Snoring (PATS; '*The impact of treatment of mild sleep-disordered breathing in children's health'*) is to provide high quality evidence regarding the effects of surgical intervention versus watchful waiting (observation) on a group of healthy children with nocturnal obstructive symptoms whose polysomnograms demonstrate mild oSDB. This study was specifically designed to evaluate the effectiveness of AT as well as associated healthcare utilization (HCU) in children with mild oSDB. In this article, we present the PATS protocol (version 19; February 19, 2019) and describe the unique challenges in designing a RCT of a surgical intervention in young children including selecting appropriate outcomes, determining approaches for collection of HCU data across geographically diverse US sites, and optimizing data collection in studies of young children.

METHODS AND ANALYSIS

Study Overview

PATS is a multi-center, randomized, single-blinded 12-month intervention study that compares the impact of AT on measures of behavior, quality of life, sleep-related symptoms, polysomnographic findings, and HCU in children with mild oSDB (Figure 1). Children with symptoms of mild oSDB are recruited from each site's otolaryngology, sleep, pulmonary, and/or general pediatric clinics. At baseline, participants undergo neurobehavioral testing and polysomnography (PSG) and assessment of patient-reported outcomes (sleepiness, quality of life, sleep quality), anthropometry, and blood pressure. All measures are repeated at 6 and 12 months, except that the PSG is only repeated at 12 months. In addition to baseline, 6-month, and 12-month visits, participants receive monthly telephone calls to maximize retention and to collect interim data on symptoms and HCU. The study started enrollment in June 2016. As of August 26, 2019, 344 children have been randomized. The reporting of the PATS protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) reporting guidelines[11], which were developed in 2013 to establish the minimum content of a clinical trial protocol.

Study Aims and Endpoints

The primary objectives are to determine the effect of early AT (eAT) versus Watchful Waiting with Supportive Care (WWSC) on a co-primary outcome: executive function assessed by a parent behavior rating (Behavior Rating Inventory of Executive Function Global Executive Composite, second edition or preschool version; BRIEF2/P GEC[12 13]), and children's sustained

attention or vigilance as assessed by signal detection parameter (d-prime) for performance on the Continuous Performance Test (CPT) from the Go-No-Go task[14].

The secondary objectives are to determine the effect of eAT versus WWSC on oSDB symptoms and quality of life. We also will track and compare group changes in HCU occurring within each site's medical system and externally, as well as filled prescriptions. Exploratory analyses propose assessment of changes in anthropometry and blood pressure, and identification of factors that moderate the response to AT.

Secondary outcomes include measurements from a range of domains: objective performance testing, behavioral scales, quality of life, physical examination, and healthcare utilization. Potential effect modifiers to be evaluated include demographics, sleep duration and efficiency, asthma/atopy measures, second-hand smoke exposure, and measures of family functioning. A detailed list of these outcomes and assessment procedures is provided in Table 1.

Study Organization

The study is supported by a Data Coordination Center (DCC)/Sleep Reading Center (Brigham and Women's Hospital; Boston, MA), charged with development of the study's statistical design and monitoring plans, construction and management of the study database and study materials, and generation of statistical reports to investigators and the PATS Data and Safety Monitoring Board (DSMB). The Sleep Reading Center is charged with centralized PSG scoring and generation of standardized PSG variables. A surgical quality assurance core is based at the University of Michigan, Ann Arbor, MI. A neuropsychology core is provided by psychologists at two sites (Children's Hospital of Philadelphia PA and Nationwide Children's Hospital Research Institute, Columbus, OH).

The study is also supported by a Clinical Coordinating Center (CCC), Children's Hospital of Philadelphia, PA, charged with overseeing the activities at the clinical sites, regulatory approvals, and providing clinical expertise. Clinical sites are each headed by a sleep medicine physician or an otolaryngologist and, together with their local research team (study coordinators, sleep laboratory staff) are responsible for recruitment and follow-up of participants. Initially, 5 clinical sites (Children's Hospital of Philadelphia, PA; Cincinnati Children's Medical Center, OH; Rainbow Babies & Children's Hospital at University Hospitals – Cleveland Medical Center, OH; University of Michigan Health System, Ann Arbor, MI, University of Texas Southwestern Medical Center, Dallas, TX) were identified to participate in the study. In July 2018, two new sites (Children's Hospital, Boston, MA; Children's Hospital of the King's Daughters, Norfolk, VA) were added to improve subject accrual. In June 2019, Boston Children's Hospital was closed to accrual upon DSMB's recommendation due to its slow accrual, resulting in 6 recruitment sites.

Study governance is through a Steering Committee with representation from each participating site, key quality control cores, and National Health Lung Blood Institute (NHLBI) program staff. An Executive Committee, consisting of the Study Chair, the DCC Directors, CCC Director, and the NHLBI project officer, who regularly meets by telephone to address emerging issues. Sub-committees are organized to address the multiple quality control and monitoring needs of the study: Surgical Quality Control, Neuropsychology Quality Control, Polysomnography Quality, Recruitment and Operations, and Publications and Presentations. An independent Data and Safety Monitoring Board (DSMB), with expertise in pediatric ethics, surgery, sleep apnea, clinical trials, and biostatistics, appointed by and reporting directly to the NHLBI, reviews quarterly reports and meets semi-annually to assess the emerging data and make

recommendations. A board-certified pediatric sleep medicine physician is continuously available as an independent medical monitor (MM).

Sample Population and Enrollment

This study recruits children with symptoms of mild oSDB and their caregivers. The inclusion criteria are: 1) Ages 3.0 to 12.9 years at the time of screening; 2) Diagnosis of mild oSDB defined as: a. Parent report of habitual snoring that occurs most of the night on at least 3 nights per week, and has been present for at least 3 months (on average occurring > 3 nights per week or more than one-half the sleep time) and b. Obstructive apnea index < 1/hour and obstructive apnea-hypopnea index <3/hour and no oxyhemoglobin desaturation < 90% in conjunction with obstructive events, confirmed on nocturnal, laboratory-based PSG; 3) Tonsillar hypertrophy ≥ 2 based on a standardized scale of 0-4; 4) Determined to be a candidate for AT by ENT evaluation ; and 5) Primary indication for AT is nocturnal obstructive symptoms. As in all RCTs, equipoise about randomization in PATS is required on the part of participants, their families, and their clinicians (ENT surgeons).

The exclusion criteria are: 1) Previous tonsillectomy; 2) Recurrent tonsillitis that merits prompt AT per the American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guidelines [3]; 3) Severe obesity (body mass index; BMI z-score ≥ 3); 4) Severe chronic health conditions that might hamper participation or confound key variables under study, include but not limited to: a) severe cardiopulmonary disorders; b)bleeding disorders; c) sickle cell disease; d) epilepsy requiring medication; e) other severe chronic health problems such as diabetes or narcolepsy; e) mental retardation or assigned to a self-contained classroom for all academic subjects; f) known genetic, craniofacial, neurological or psychiatric conditions likely to

affect the airway, cognition or behavior; g) psychiatric or behavioral disorders requiring or likely to require initiation of new medication, therapy or other specific treatment during the 12-month trial period (other than ADHD). Children with ADHD are included; but those with autism spectrum disorder or those with global development impairment are excluded; 5) Current use of psychotropic medication (other than medications for Attention-Deficit Hyperactivity Disorder (ADHD)), hypnotics, antihypertensives or growth hormone; Chronic corticosteroids are allowable, although children with a burst of oral corticosteroid therapy for asthma are deferred until corticosteroids are no longer prescribed and it has been 30 days since last dose. Medication use during the study is captured on a monthly basis via phone or in-person interviews using a structured case report form completed by research coordinators. In addition, prescriptions that are filled within the local medical system are captured by accessing healthcare utilization data on a quarterly basis; 6) History of severe developmental disability or ABAS (Adaptive Behavioral Assessment System) score < 60; 7) Parent/guardian unable to accompany the child on the night of the PSG; 8) Family planning to move out of the area within the year; 9) Family does not speak English or Spanish well enough to complete the behavioral and performance measures; 10) Child in foster care.

Study Interventions

Depending on the randomized treatment assignment, participants are assigned to either WWSC or eAT. Within 4 weeks of randomization, participants randomized to the eAT arm undergo surgery under general anesthesia, as part of routine clinical care. Surgery is performed by board-certified otolaryngologists with or without the assistance of resident physicians in accredited otolaryngology training programs. Prior to the surgical procedure, tonsillar size is graded using a

standardized scale of 0-4[15]. Extent of adenoid tissue is graded as mild (0- 33%), moderate (34-66%) or severe (67-100%) obstruction of the posterior choanae intra-operatively in subjects undergoing AT. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue are performed by cold dissection, monopolar electrocautery or any other recognized surgical technique.

Regardless of the treatment assignment, all participants receive sleep and healthy lifestyle education. Standardized materials recommended by the National Institutes of Health and pediatric professional sleep societies are used to reinforce optimal sleep health and educational play is encouraged by providing take-home materials addressing sleep health. Other supportive care is provided at initial evaluation and as needed throughout the course of the trial. For example, participants identified as having suboptimal asthma or nasal allergy control will be referred to their primary care physician for management and further treatment of these problems.

After 12 months, children who did not undergo AT who have a 12-month PSG showing concerns for oSDB or whose parent reports ongoing symptoms/concerns are referred back to ENT for further clinical management (such as AT, if still indicated) as per standard clinical care.

Blinding

As in CHAT[16], the use of a surgical intervention prevents blinding of the child, parent, and certain staff members because performing sham surgery in children raises ethnical and feasibility concerns. PATS adopts a similar approach where the principal investigators at each site (other than sites at which the PI is a surgeon), and study coordinators who directly collect primary outcomes are blinded to study treatment. In addition, all DCC and CCC staff except for those responsible for statistical analyses, data management, and AE adjudication and communication

are blinded. The responsibilities of blinded and unblinded staff at each site has been clearly delineated and a structured format for communication was established to minimize the impact of the unblinding on study outcomes and study progress.

Neuro-behavioral Testing

To ensure reliable collection of neurobehavioral test data, much attention was directed at developing a rigorous protocol for training research assistants to properly administer the tests. Initial training was provided by in-person review and demonstration of procedures. Examiners later reviewed administration procedures, practiced the assessments with other team members, and made video recordings of an assessment conducted with a child volunteer. To ensure fidelity of test administration, the videos were reviewed by one of the two psychologists in the Neurobehavioral Core, with feedback provided and additional assessments required if procedures did not meet specific competency criteria. The challenge in testing young children, some of whom had limited attention spans and difficulty in following through on test instructions, was addressed by selecting engaging tests that were "hands-on" and could be easily understood by children as young as 3 years. Testing procedures included defined opportunities for children to practice, with repetition of instructions. Recognizing that despite these procedures, there would still be some variation in engaging children, protocols were developed to allow the examiners to document behaviors that may have contributed to test performance, such as inattention or off-task behaviors (e.g., "Child pushes button repeatedly without reference to the screen").

Informatics and Data Management Core (IDMC)

PATS is supported by an innovative Informatics and Data Management Core (IDMC) that develops and integrates cutting-edge, open-source web development tools and dynamic

research data, providing robust and highly interactive tools for multicenter studies, clinical trials and data repositories. These tools are developed and updated on a weekly basis using a continuous deployment methodology based on the agile software development framework. The Core provides thorough documentation of the software and the deployment architecture in the form of online version-controlled documentation, and web-based video tutorials. Electronic data entry is supported by the software program *Slice* (https://sliceable.org), which excels at dynamic in-application reporting and provides researchers, individual clinical sites, the DSMB and the sponsor a live snapshot of the current state of the database. *Slice* also provides robust project management tools, including the ability to easily create and track participant/study schedules. Data interoperability is handled by the Spout JavaScript Objective Notation (JSON) (https://www.json.org/) data dictionary framework to modularize data definitions into small, maintainable versioned data element descriptors. Finally, the IDMC promotes data liberation, enabling researchers to export all data they have entered at any point in a useable format that can be imported into a new system of their choice.

Health care utilization (HCU) and electronic medical record (EMR) surveillance

The study addressed challenges in collecting consistent and complete HCU from multiple, diverse medical centers that utilize different EMRs and from families who may utilize health care services outside of PATS clinical sites. To comprehensively identify episodes of HCU, a surveillance approach was developed that includes the following: 1) a semi-structured interview undertaken on a monthly basis with caregivers when information is gathered regarding any HCU 'billed and filled' (that is, any healthcare encounter and any filled prescription; 2) the local EMR is queried approximately quarterly in order to ensure that no internal HCU (encounters or prescriptions within the local medical system) was missed during

caregiver interviews; and 3) attempts are made to receive medical reports based on any caregiver reports of external HCU (encounters or prescriptions outside of the local medical system that are not visible in the local EMR). Prior to study start, meta-data for common pediatric HCU events were identified to develop a standardized HCU data dictionary which was supplied to each participating site. A medical record analyst from each site was asked to develop an electronic query designed to pull appropriate data at planned intervals. HCU data are entered into a cumulative electronic log by the unblinded coordinator from each site, encompassing hospitalizations (reason, location, and number of days), unscheduled and scheduled outpatient visits, and filled medication prescriptions. Given the marked variability in EMR and resources across sites, procedures for undertaking the quarterly EMR queries vary: some sites have an analyst working directly with project staff to request a batch of data whereas other sites train coordinators to query their EMR using script developed by an analyst. The quarterly EMR queries each cover a period of four months such that there is always overlap across queries, as there can be delays in data being populated in the EMR. Completed logs (de-identified apart from the inclusion of dates) are transferred to the DCC via an encrypted data transfer method; source data are maintained on a secure server at each site.

Statistical Considerations

A total of 460 children are randomized to one of the two treatment arms in a 1:1 ratio. Factors identified to possibly influence treatment response include child's age (reflecting developmental differences in neuro-behavior and potential sensitivity to oSDB), weight status (a co-morbidity that may portend less effective surgical responses) and race (based on prior data indicating suboptimal surgical response of African American compared to white children)[5]. Therefore, randomization is stratified by the following factors within site: age (< 5 years vs > 5

years); overweight status (body mass index [BMI] >85th percentile); and race (African American vs other). Stratification provides greater assurance that the comparison groups will be similar with respect to these variables. However, given the overall sample size of 460 and the relatively large number of strata (8 strata within each of the 7 sites), the expected total number of subjects within each stratum is too small (about 8) to use standard randomization approaches such as permuted blocks. To ensure that treatment arms are balanced with respect to these factors as well as for the number of subjects in each group, we use a dynamic randomization method, Pocock and Simon's minimization method [17]. Specifically, for each eligible participant, based on the value of his/her stratification factors, the participant will have a 30% chance to be allocated randomly to one of the two treatment arms, and a 70% chance to be allocated to the arm that minimizes the differences in number of participants across two treatment arms within each stratum deterministically. We have implemented this randomization algorithm in our Data Management System (Slice).

In CHAT, greater improvements in the BRIEF score were observed in the eAT vs WWSC arm but we could not rule out the possibility that these improvements were influenced by parental expectations. Therefore, in PATS, we elected a co-primary outcome that included one objective, performance-based neurocognitive measure (the GNG d-prime score for sustained attention) and one composite behavioral outcome (the BRIEF2/P GEC score). To maintain a study-wise significance level of 5% for analysis of co-primary endpoints, we use a sequentially rejective method, the Holm's method, which has been shown to be uniformly more powerful than the Bonferroni procedure. In the case of two tests using an overall alpha of 0.05, the comparison with the largest difference will be tested at the 0.025 level. If it is rejected, the comparison with the second difference will be tested at the 0.05 level. For the BRIEF score

change from baseline to 12 months, we used prior CHAT data and assumed a relatively large 3.7 points difference in change scores between the two arms, a 11.5 points standard deviation at baseline and a correlation between the baseline and the follow-up measurements of 0.73. For the GNG change score, we assumed a smaller 0.33 difference between the two arms, a baseline standard deviation of 0.77, and a correlation between baseline and follow-up measurements of 0.48[14]. Based on the experience in the CHAT study, we assume a drop-out rate of 15% at 6 months, and an additional 5% attrition at 12 months. Using these estimates and methods described in Hedeker et al.[18] for sample size estimation for longitudinal designs with attrition, we estimated a total sample size of 460 participants, resulting in 390 and 368 evaluable subjects at 6 and 12 months, respectively. Our sample size with the assumed attrition rate has 98% power to detect a difference of 3.7 points in the BRIEF 2/P GEC change score and 98% power to detect a difference of 0.33 points in the GNG change score between treatment groups at a significance level of 2.5% and 5%, respectively. In designing this study, we chose the sample size so that the study will have ample power for testing the primary and key secondary hypotheses and adequate power to detect moderate to large moderation effects.

Primary analyses will follow the "intention-to-treat" principle and use a mixed effects model relating outcomes and treatment group indicators. Time (0, 6, and 12 months) will be modeled as a categorical variable to allow separate comparisons of intervention effect at 6 and 12 months. Missing data will be handled through multiple imputation[19] or inverse probability weighting[20]. Continuous secondary outcomes will be analyzed in the similar fashion as the primary outcome. For endpoints related to HCU, we will consider models that account for potential data dispersion and possible preponderance of zeros (e.g., zero-inflated negative

binomial models). Statistical tests of treatment by covariate interaction will be performed to assess whether treatment effect varies by age, baseline weight, atopy/asthma status, second-hand smoke, socioeconomic status, family functioning, or race.

Safety and Data Monitoring

The study is monitored routinely for issues of data quality, study conduct (including recruitment and follow-up rates), data quality, and adverse events. Of particular concern are attrition and cross-over rates which, if excessive, could jeopardize the integrity of the study. A special category of event, denoted as "treatment failure" was utilized in the CHAT study and is also used in PATS. Treatment failures are identified using pre-specified thresholds for defining changes in behavior or health likely attributable to persistent mild oSDB, adjudicated by an independent medical monitor. Adverse event surveillance, adjudication, and reporting follows the requirements of NHLBI and the central reliant IRB at CHOP, as well as any site-specific IRB requirements. Quarterly reports addressing these issues of study conduct, data quality, adverse events and treatment failures are provided to the Steering Committee, the DSMB and NHLBI. Given that the patient population consists of children who are otherwise healthy, with mild oSDB, and that the intervention is considered a standard clinical intervention, we do not anticipate that the interim analysis will yield efficacy data compelling enough to require early termination. Therefore, we will monitor the BRIEF2/P GEC score and GNG score, the co-primary outcomes, in planned interim analyses of efficacy. We plan to perform one interim analysis after half of the study population has completed their 12-month evaluations. Based on our recruitment projections, most of the accrual will be complete at this time and therefore early stopping may not be relevant. To create a formal framework for assessment of interim results, the Haybittle-Peto boundary will be used [21]. That is, interim results for comparisons of the

BRIEF2/P score and GNG score between treatment groups will be considered sufficient to consider early termination only if at least one of the between group differences are statistically significant using a family-wide significance level of 0.001. The Haybittle-Peto stopping rule allows the final analysis to be evaluated at a 5% level of significance [21 22].

Patient and Public Involvement Statement

The design of this study is informed by the experience of participants and their families in the CHAT study, where study staff heard of interest in understanding the impact of snoring on quality of life and cognition. The teachers of the participating children provided standardized neurobehavioral assessments during the course of the study. The conduct of the study is overseen by the DSMB that includes representatives from the National Institutes of Health. We plan to use data from this study to disseminate information directly to patients through educational modules, blogs and an on-line forum available in a sleep apnea patient portal (MyApnea.Org)that has enrolled over 17,000 patients and their family members to learn more about sleep apnea and ongoing sleep apnea research.

ETHICS and DISSEMINATION

The potential consequences of deferring surgery and treating oSDB conservatively are unclear, and provide the rationale for this randomized controlled trial. There is great physician and geographical differences regarding whether or not oSDB is treated surgically. In many centers, children with a normal PSG do not undergo AT and in other centers, children who snore do not undergo PSG (precluding distinction of OSA from oSDB). All options, including refusal to be in the study in order to obtain more immediate treatment, as well as potential risks of surgery, will be discussed with the participants and their families. At the end of the trial, participants will have

a final PSG, and children with persistent symptoms of SDB or new abnormalities on PSG will be referred for clinical management.

The study protocol, IRB# 14-011214, was approved by the institutional review board at Children's Hospital of Philadelphia (CHOP) on October 3rd, 2014. Following NIH policies, it was decided that the CHOP IRB would be the study's single central IRB. Participating sites provided reliance agreements allowing the CHOP IRB to act as the IRB of record for their institutions. The relying institutions remain responsible for ensuring compliance with the CHOP IRB's determinations and with the Terms of its Office of Human Research Protections – approved Federal Wide Assurance. The approval of CHOP as the central IRB of record was granted on February 29, 2016. Each clinical center is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its IRB. Informed consent (signed and dated by the participant's parent/guardian) must be obtained prior to initiation of any study related activity.

Proposed protocol changes are presented to the Steering Committee 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 CCC and DCC will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol. Substantive changes to the protocol require approval from the DSMB before implementation.

To maintain patient confidentiality, participants are identified to the DCC only by patient identification numbers and no personal information will be transmitted to the DCC. Furthermore, data for reports and publications will be provided in aggregate or blinded form without the

identification of individual patients. At the clinical sites and participating centers, all data will be: 1) kept in confidential locked files; 2) identified by participant identification number only; 3) kept separately from identifying information used for participant tracking and follow-up contacts.

The results will be published in peer-reviewed journals and presented at academic conferences, as well as directly to patients through a web portal MyApnea.org. The data collected from the PATS study will be deposited in a repository (National Sleep Research Resource; sleepdata.org) after completion of the study to maximize use by the scientific community.

DISCUSSION

Mild oSDB is of great clinical and public health relevance given its high prevalence and potential impacts to health and well-being of children, their families, and the health care system. A paucity of data from randomized clinical trials has led to fundamental questions regarding the role of AT in children with mild oSDB, contributing to large geographical variations in care and potential for surgery to be both over- and under-utilized. PATS was designed to resolve uncertainties on management approaches for pediatric mild oSDB by addressing several critical issues: a) assess outcomes of importance to children and their families - in particular, the patient-reported outcomes of behavior, quality of life, and sleep disturbances; b) examine differences in treatment responses among children who are at increased risk for mild oSDB, such as pre-school children, minorities, and children with asthma or obesity; c) evaluate HCU as an under-studied outcome in this condition; and d) assess moderating influences of second-hand smoke, insufficient or irregular sleep, socioeconomic status (SES) and family functioning. Meeting the study goals requires collection of a large variety of data from multiple sources (child, caregiver,

teacher, and neighborhood geocode) and across multiple domains (neurobehavior, polysomnography, actigraphy, sleep-related symptoms, quality of life, anthropometry, blood pressure, health care utilization, cotinine, immunoglobulin titers).

Several challenges present in the design of PATS. 1) The targeted study population include children aged from 3.0 to 12.9 years at the time of screening. In accord with the rapid development of children in this age range, age-specific forms are available for both the BRIEF and GNG tests. Therefore, the tests given at each visit are age-dependent. During the 12-month follow-up period, children may move from one age group to another age group, resulting in different age-specific tests used at baseline and at the 12-month follow-up. However, the test scores are normalized to each age category making them comparable across different groups. Furthermore, age has been chosen as a stratification factor to ensure balance across treatment arms within each age category. Effect modification by age will also be examined as a pre-specified subgroup analysis. 2) Recall bias may present, especially when reporting behavior problems; parents may differ in their vigilance in monitoring their children's behavior problems or adverse events in general and willingness to discuss these issues with the study coordinator, and such differences may not be balanced by treatment arm. When analyzing safety data, sensitivity analyses may be needed to quantify the potential effect of such bias. 3) Double-blinding is not possible in a study of surgical treatment in children. Parents and children cannot be feasibly blinded to surgery. The use of a caregiver-reported outcome is of concern in this setting as responses may reflect treatment expectations. We attempted to address this concern by including an objective test (GNG) as a co-primary outcome as well as collecting comparable behavioral data from the child's teachers, who may be unaware of treatment. To minimize bias due to unblinded staff, we established structured communication protocols between blinded and

unblinded personnel at each site. Nonetheless, unblinding may occur especially considering the study's frequent contact points between parents and study personnel (three visits and monthly phone calls). Every effort is made to prevent unblinding and any unblinding episodes are documented to facilitate the interpretation of study findings. 4) As in any clinical trial, cross-over and loss to follow-up will be inevitable despite attempts at best practice. While cross-over does not threaten the validity of the intent-to-treat primary analysis, it may dilute the treatment effect and reduce the study power. The rate of cross-over is closely monitored and its effect on study power will be assessed. 5) HCU data are from diverse academic health care centers in the U.S. where costs are difficult to directly assess due to the discrepancies between costs and charges. Therefore, our analyses will quantify key HCU events (e.g. hospitalizations, clinic visits, medications, etc), which will provide a proxy for costs.

In summary, PATS will provide evidence on whether children with mild oSDB benefit from surgery, by randomizing children to the two most common managements: adenotonsillectomy or observation. The findings will have key implications for disease management, including the need for pre-operative PSGs to distinguish oSDB from obstructive sleep apnea, the potential to reduce practice and geographic variability in the management of oSDB, and the understanding of response to surgery in African American children and in lower socio-economic status families, in order to optimize their management and reduce health disparities. Moreover, the design of PATS provides a model for conducting a surgical trial in children across a large age range studied with both caregiver reported and objectively measured outcomes, while also assessing a wide range of other outcomes such as HCU and potential effect modification by several host and environmental factors. Salient statistical considerations include plans for analysis of a co-primary outcome without excessive loss of power; use of a dynamic

randomization method to address multiple strata of interest in the context of a modest sample size; analysis of complementary caregiver and teacher reports; and interim safety analyses that minimally impact study power.

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AUTHOR CONTRIBUTIONS

All authors (Rui Wang, Bakker, JP, Ronald D. Chervin, Susan L. Garetz, Fauziya Hassan4, Stacey L. Ishman, Ron Mitchell, Michael Morrical, Syed K Naqvi, Jerilynn Radcliffe, Emily I. Riggan, Carol L. Rosen, Kristie Ross, Michael Rueschman, Ignacio E. Tapia, Hudson Gerry Taylor, David A. Zopf, Susan Redline) drafted and revised sections of the study protocol according to their expertise. First draft of the manuscript: Rui Wang and Susan Redline. All authors critically reviewed and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

Dr. Bakker is a full-time employee of Philips, a company that focuses on sleep and respiratory care. Dr. Bakker also has a part-time appointment at Brigham and Women's Hospital. Dr. Bakker's interests were reviewed and are managed by BWH and Partners HealthCare in accordance with their conflict of interest policies. Dr. Chervin reports service on the boards of the American Academy of Sleep Medicine, Associated Professional Sleep Societies, American Board of Sleep Medicine, American Academy of Sleep Medicine Foundation, International Pediatric Sleep Association, and the not-for-profit Sweet Dreamzzz. He serves as an author and editor for UpToDate. Dr. Hassan received research funding from Jazz pharmaceuticals and is a consultant for Biogen (Spinraza); none is relevant to this manuscript. Dr. Rosen is a member of American Academy of Medicine and the American Academic of Sleep Medicine Foundation Board of Directors. She received institutional research funding from Jazz Pharmaceuticals and from Flamel (Avadel) Pharmaceuticals, unrelated to the submitted work. Dr. Ross reports non-financial support from Boehringer Ingelheim, grants and non-financial support from TEVA, non-financial support from GSK, non-financial support from Merck, grants from Flamel, grants from Jazz, and grants from Astra Zeneca, outside the submitted work. Dr. Redline received institutional grants from Jazz Pharmaceuticals and consulting fees from Jazz Pharmaceuticals and Respicardia. The other authors have no financial conflicts of interest.

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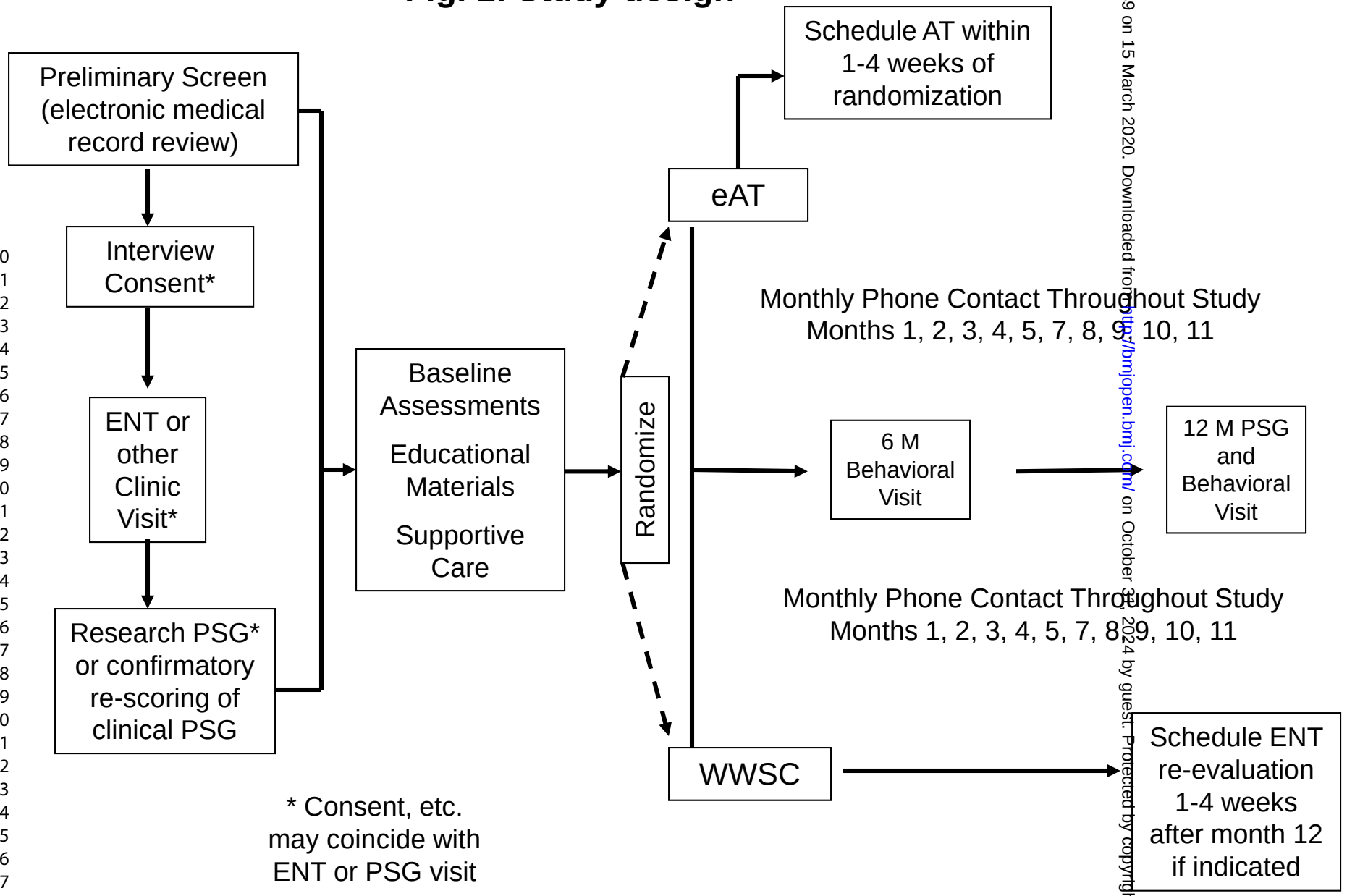
Table 1. Primary, secondary endpoints, pre-specified candidate moderators.

Primary endpoints	BRIEF2/P Global Executive Composite Score[12 13]
	GNG sustained attention d-prime parameter[14]
Secondary endpoints	
Objective performance testing	GNG inhibitory control d-prime[14]
	Fine motor coordination: NIH-Toolbox 9-Hole Pegboard Dexterity Test
Behavioral scale	Executive function: BRIEF 2/P meta-cognition and emotional regulation summary scores and subscales for parent and teacher reports
	Behavior: Child Behavior Checklist (CBCL)[23] summary scale and subscores, parent and teacher ratings
	Attention: Conners 3 Short Form (caregiver and teacher versions) Global Index T score and subscales[24]
SDB symptoms	Pediatric Sleep Questionnaire: Sleep-Related Breathing Disorder (PSQ-SRBD) Scale total score[25]
	Sleepiness: Epworth Sleepiness Scale modified for children summary score and PSQ-SRBD sleepiness scale[26]
	Snoring: The Patch Snoring Sensor
Quality of life	Generic: Pediatric Quality of Life Inventory (PedsQL) total score and subscores[27]
	Disease specific: OSAS-18 total score
Physical exam	Measurements of weight; height; body mass index (BMI); waist, hip, neck circumferences
	Systolic, diastolic and mean blood pressure levels
Health Care Utilization	Medications, health care visits (scheduled, unscheduled), ascertained from caregiver reports, EMR surveillance, billing and pharmacy records, hospitalizations
Potential Effect Modifiers	

Demographics	race, SES (parent education, family income, financial stress rating scale, geocode data on neighborhood characteristics)
Sleep duration and efficiency	objective assessment by 7-day wrist actigraphy
Asthma/atopy	IgE, International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, review of EMR and parent interview (using NHLBI asthma definitions based on a history of asthma and use of asthma medications)
Second-hand smoke exposure	urinary cotinine
Family functioning cluster	family functioning (Family Assessment Device, short form); parenting style (Parenting Style Questionnaire); parent perception of stress (Parenting Stress Index 4th ED., short form); medical literacy (Rapid Estimate of Adult Literacy in Medicine, Revised); discrimination (Experiences of Discrimination)

Figure 1. An Overview of Study Design.

Fig. 1: Study design



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	23

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8,9,17,18
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5,6
Objectives	#7	Specific objectives or hypotheses	7,8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7,14,15
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	8,9

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9,10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14,15
Recruitment	#15	Strategies for achieving adequate participant enrolment	15

		to reach target sample size	
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11,12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference	12,13,14

		to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16,17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17,18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17,18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	17,18

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19,20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23,24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing	20

		arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	S1-17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a