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| Title: | **Investigating the experience of living with Down syndrome and obstructive sleep apnea syndrome** |
| Short Title | DS and OSAS |
| Sponsor: | Children's Hospital of Philadelphia |
| eIRB Number | |
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## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse event |
| AT | Adenotonsillectomy |
| DS | Down syndrome |
| OSAS | Obstructive sleep apnea syndrome |
| PAP | Positive airway pressure |

## ABSTRACT

Context: (Background)

- OSAS is very common in children with DS
- OSAS in children with DS does not resolve after adenotonsillectomy
- Many children with DS and OSAS require treatment with PAP

Objectives: (primary and important secondary objectives)

- Identify the perceptions, beliefs, and family-relevant outcomes regarding the treatment of OSAS with PAP in children with DS

Study Design:

- Cross-sectional study

Setting/Participants:

- The study will be performed at CHOP and Cincinnati Children's Hospital Medical Center (CCHMC)outpatient setting
- Caregivers of children with DS and OSAS aged 6-17.5 years treated with PAP

Study Interventions and Measures:

- Open-ended semi-structured interviews

## TABLE 1: SCHEDULE OF STUDY PROCEDURES

| **Study Phase** | **Screening & Interview** |
|---|---|
| Informed Consent | X |
| Review Inclusion/Exclusion Criteria | X |
| Semi-structured open-ended interview | X |

# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Down syndrome (DS) is a common disorder, occurring in 1 per 800 births,[1-3] which translates to approximately 5,400 children with DS born in the USA annually. [4] Hallmarks of the syndrome include intellectual disability, hypotonia and craniofacial anomalies, and congenital cardiac defects occur in 50% of individuals.[5] Common comorbidities include hypothyroidism, obesity, and the obstructive sleep apnea syndrome (OSAS). Untreated OSAS is associated with significant morbidity such as growth failure,[6] systemic,[7-9] and pulmonary hypertension,[10,11] endothelial dysfunction,[12,13] and cognitive and behavioral deficits.[14-19] Median life expectancy in individuals with DS has increased from 25 years in 1983 to 58 years[20,21] in the present day. While this represents a significant advance in health, individuals with DS still have early mortality compared to the general population. It is therefore incumbent upon health care practitioners to diagnose and treat comorbidities, such as OSAS, in order to optimize health and cognitive/behavioral function, increase survival, and maximize health-related quality of life. Individuals with DS are predisposed to OSAS due to craniofacial features (midface hypoplasia, glossoptosis), hypotonia, comorbid obesity, and hypothyroidism.[22] Studies have shown a prevalence of OSAS in children with DS between 45 and 55%.[23-25] These rates are markedly higher than that of typically developing children[24,25] in whom the prevalence of OSAS is about 2%.[26]

Adenotonsillectomy (AT) is considered first-line treatment for childhood OSAS.[27] However, available data indicate that polysomnography (PSG) improves in only a portion of children with DS after AT.[28] In fact, many children with DS are referred for positive airway pressure (PAP) therapy initiation due to persistent OSAS after AT, and PAP appears to be an important feature of the experience of living with DS.[29] PAP has been shown to be highly effective at resolving polysomnographic manifestations of OSAS in children and adolescents, including those with DS and other disabilities.[30,31] However, PAP as a treatment for OSAS has not been well-studied in children with DS. Furthermore, patient/family reported outcomes are an important knowledge gap long overdue in this population.

## 1.2 Relevant Literature and Data

**DS Prevalence and morbidity**: Down syndrome (DS) is a common disorder, occurring in1 per 800 births,[1-3] which translates to approximately 5,400 children with DS born in the USA annually.[4] Hallmarks of the syndrome include intellectual disability, hypotonia and craniofacial anomalies. Congenital cardiac defects occur in 50% of individuals.[5] Common comorbidities include hypothyroidism, obesity, and obstructive sleep apnea syndrome (OSAS). DS is also associated with premature death and early-onset Alzheimer's disease.[32] Median life expectancy has increased from 25 years in 1983 to 58 years [20,21] in the present day. While this represents a significant advance in health, individuals with DS still have early mortality compared to the general population.

**DS and OSAS**: Individuals with DS are predisposed to OSAS due to craniofacial features (midface hypoplasia, glossoptosis, hypotonia), comorbid obesity, and hypothyroidism.[22] Studies have shown a prevalence of OSAS in children with DS between 45 and 55%.[23-25]

These rates are markedly higher than that of typically developing children [24,25] in whom the prevalence of OSAS is about 2%.[26] Untreated OSAS is associated with significant morbidity such as growth failure,[6] systemic[7-9] and pulmonary hypertension,[10,11] endothelial dysfunction,[12,13] and cognitive and behavioral deficits.[14-19] It is therefore incumbent upon health care practitioners to diagnose and treat comorbidities, such as OSAS, in order to optimize health and cognitive function, increase survival, and maximize health-related quality of life in youth with DS and OSAS.

**Treatment of OSAS in Children with DS**: Given the high prevalence of OSAS, the American Academy of Pediatrics published a clinical report focused on the care of children with DS in 2011.[5] In this guideline, they advised families to assess for OSAS as soon as 6 months of age and emphasized the poor correlation between parental history and sleep study results. Therefore, they recommended that all children with DS undergo a sleep study by 4 years of age, and that pediatricians discuss the impact of obesity as a risk factor for OSAS. Adenotonsillectomy (AT) is considered first-line treatment for childhood OSAS.[27] However, available data indicate that polysomnography (PSG) improves in only a portion of children with DS after AT.[28] In fact, many children with DS are referred for positive airway pressure (PAP) therapy initiation due to persistent OSAS after AT.[29] PAP has been shown to be highly effective at resolving polysomnographic manifestations of OSAS in children and adolescents, including those with DS and other disabilities.[30,31] Importantly, studies indicate that PAP also reduces symptoms of OSAS and improves school performance, behavior, mood, daytime sleepiness and quality of life (QOL) in typically developing children and adolescents.[30,33] Another important consideration is that PSG results may not predict patient-reported outcomes and other physiological responses, indicating a need for studies that inform the medical community not only about healthcare provider-relevant outcomes but also about family-relevant outcomes related to the experience of living with DS and OSAS. In addition, RCTs that examine a range of relevant qualitative, clinical and physiological outcomes are lacking. These studies, such as the current proposal, could inform families and the medical community about variation in responses and provide the framework for developing a "precision medicine" approach for future single- or multiple-staged approaches, matching the best intervention to the individual child defined by appropriate family-relevant, clinical, physiological and/or genetic factors.

**PAP adherence in children with DS**: There is a dearth of literature regarding PAP adherence in children, and even less in children with DS.[34-36] Generally, PAP is inherently difficult for individuals to use regularly. In addition to the daily burden of putting the equipment on each night and discomfort of wearing a mask with pressurized air being administered while sleeping, common side-effects include nasal symptoms (e.g., nasal dryness, rhinorrhea, congestion and epistaxis), eye irritation, skin pressure sores or dermatitis, and aerophagia. Some patients suffer from feeling closed-in by the mask (e.g., claustrophia). Not surprisingly, PAP efficacy is limited by poor adherence.[37] Most studies in the pediatric age range have encompassed a wide age spectrum and heterogeneous populations,[29,37-39] and have reported improved adherence over time.[29,39] Importantly, the few studies, all retrospective, including children with DS under the larger umbrella of children with developmental disabilities (DD), have shown better adherence in children with DD compared to typically developing children.[29,39] Hawkins et al reported that DD was a positive predictor factor for PAP adherence (OR = 2 .55, 95%CI = 1.27–5.13; p = 0.007),[29] and our group has showed that at 3 months after PAP initiation, adherence was 86.7% [33.9-

97.9%] of nights in children with developmental disabilities and 62.9% [30.8-87.8%] in typically developing children (p=0.01).[39]

### 1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators at CHOP and CCHMC will perform the study in accordance with this protocol. CHOP investigators will obtain verbal consent, CCHMC will obtain written consent, and will report unanticipated problems involving risks to subjects or others in accordance with Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

The purpose of this multi-center study is to further characterize the experience of living with DS and OSAS.

### 2.1 Primary Objective (or Aim)

- The primary objective of this study is to identify the perceptions, beliefs, and family-relevant outcomes regarding the treatment of OSAS with PAP in children with DS.

## 3 INVESTIGATIONAL PLAN

### 3.1 General Schema of Study Design

Cross-sectional study

### 3.2 Study Duration, Enrollment and Number of Sites

This is a multi-center outpatient study to be performed at 2 clinical sites: Children's Hospital of Philadelphia and Cincinnati Children's Hospital. Forty Caregivers of children with DS and OSAS treated with PAP and their children will be enrolled. The study comprises one 30-minute open-ended semi-structured interview per caregiver. The duration of the interview is approximate. It will last up to 30 minutes as some families may want to include more details.

### 3.3 Total Number of Study Sites/Total Number of Subjects Projected

#### 3.3.1 Duration of Study Participation

The study duration per subject will be 1 day.

#### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at two investigative sites in the United States.

Recruitment will stop when approximately 40 subjects are interviewed. It is expected that approximately 40 subjects will be enrolled to produce 30 evaluable subjects.

## 3.4 Study Population

Adult caregivers of children with DS and OSAS and their children will be the participants of this study. The inclusion/exclusion criteria below include required characteristics of the children to consider their caregiver eligible for participation.

### 3.4.1 Inclusion Criteria-Patients

1) Children with DS and OSAS treated with PAP for at least 6 months
2) Children aged between 6 and 17.5 years
3) English proficiency

### 3.4.2 Exclusion Criteria-Patients

4) In foster care
5) Diagnosed with major illness, such as leukemia or severe cyanotic congenital heart disease listed for cardiac transplant as these severe diseases may add confounders

### 3.4.3 Inclusion Criteria-Caregivers

6) Parent or legal guardian of an eligible patient subject
7) English proficiency
8) Must live with the patient subject at least 4 nights of the week

### 3.4.4 Exclusion Criteria- Caregivers

9) Foster parent

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

## 4.1 Screening and Interview

- Informed Consent
- Medical record review
- One semi-structured 30 minute open-ended interview per participant will be conducted over the phone. The interview will be audio-recorded

#### 4.1.1 Visit 1

- Open-ended semi-structured interviews will be conducted over the phone and audio recorded.

### 4.2 Unscheduled Visits

Due to the nature of this study, unscheduled visits are not expected

### 4.3 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator if they fail to keep the phone interview appointment repeatedly. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

#### 4.3.1 Early Termination Study Visit

Subjects who withdraw from the study will not have the interview as this is the only study procedure.

## 5 STUDY EVALUATIONS AND MEASUREMENTS

### 5.1 Screening and Monitoring Evaluations and Measurements

#### 5.1.1 Medical Record Review

- Date of birth of child
- Race, ethnicity, maternal education of child and parent
- Zip code of the family
- Sleep study results of child
- PAP information of child: date of initiation of treatment, titration study, adherence

- Child comorbidities

## 5.2 Interview

Semi-structured interviews will explore such key constructs as knowledge/belief about OSAS and PAP therapy, routines and resources that promote or limit PAP use, barriers, self-efficacy, and communication and attitudes about PAP. The interviews will be performed with the parent and that they will be audio-recorded.

## 5.3 Safety Evaluation

Data safety will be strictly monitored during the study. Because of the nature of the study, no other safety issues are anticipated.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Primary Endpoint

The primary endpoint will be completing the interviews.

## 6.2 Control of Bias and Confounding

For this mixed methods research, all caregivers meeting criteria will be contacted. The first forty confirming participation and providing consent will be included in the study.

## 6.3 Statistical Methods

### 6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### 6.3.2 Analysis of Interviews

Data Analysis: Interviews will be transcribed by Datagain, a professional transcription company. Audio files are loaded onto a secure site. In the process of transcription, all identifying information will be removed. Password protected transcripts are returned to the Mixed Methods Research Lab where they are loaded into a password protected NVivo file on a secure server in the Department of Family Medicine and Community Health. Datagain has a business use agreement with the University of Pennsylvania. Once transcripts are verified for accuracy, the audio file will be destroyed. The study team will create a codebook by conducting a line by line reading of the first five transcripts. The investigators will identify key ideas in the transcripts and will use these key ideas to form codes. Each code will be operationalized and decision rules for their application will be included in the definition. Once the codebook is stabilized, the team will double code the first five transcripts and will use the interrater reliability function in NVivo to ascertain agreement.

Once 95% agreement has been achieved, the team will code the remaining transcripts, checking interrater reliability every fifth transcript.

Coded data will be summarized, examined for patterns and used to identify factors associated with adherence and non-adherence as well as implementation.

### 6.4 Sample Size and Power

In qualitative research, sample size is dictated by the principle of saturation. Saturation is when no new themes arise among each of the key subgroups in the sample. Several factors dictate an estimation of when saturation might be achieved. Key among these is the degree of homogeneity within the sample. Since the families we will recruit are all dealing with a similar set of issues and similar clinical contexts, we anticipate that saturation will be likely with up to 15 families per site.[40] We will conduct our analysis concurrent with data collection, using the constant comparative method. In this approach, we iteratively move between codes and texts, constantly looking for examples of existing ideas and being alert to new ones. This process enables us to learn when no new ideas emerge within the group as a whole and within each site. Although in our experience we typically achieve saturation with approximately 15 interviews per group, we have allowed for up to 20 interviews per site so that we can assure that saturation has been achieved.

## 7 SAFETY MANAGEMENT

### 7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

### 7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format.

## 8 STUDY ADMINISTRATION

### 8.1 Data Collection and Management

1. Confidentiality. Password protected transcripts will be saved into a password protected NVivo file on a secure server at CHOP. Access to data will be limited to study team members. Demographic and PAP data will be entered and saved in a CHOP-based REDCap system. All identifiers will be saved in the system.

2. Security. Same as above.

3. Anonymization, de-identification or destruction. All PHI identifiers and HIPAA related documents (consents, HIPAA authorization forms) will be deleted 6 years after study completion, in accordance with Policy A-3-9.

4. All data from the semi-structured interviews will be audio recorded. Recordings will be promptly removed from portable recording devices and saved to a secure, password-protected CHOP-based computer, identified by study ID.

## 8.2 Confidentiality

No identifiable data will be used for a future study without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

## 8.3 Regulatory and Ethical Considerations

### 8.3.1 Data and Safety Monitoring Plan

- Principal Investigator: It is the responsibility of the Principal Investigator to oversee the overall safety of the study. This will include careful assessment and appropriate reporting of adverse events. Since the study procedures are not greater than minimal risk, SAEs are not expected. The PIs responsibility will be to assure that appropriate study data are communicated to the participant's family and physicians and that appropriate referrals or interventions are initiated.

- Institutional Review Board: CHOP will be the central IRB of this study. It is the responsibility of the Principal Investigator at each clinical site to provide their IRB with all pertinent material, including a copy of the informed consent. Approval from the reviewing IRB of the informed consent form must be obtained prior to screening or enrolling any participants. The clinical site's Principal Investigator also maintains the responsibility of coordinating with the central IRB in initiating protocol re-approval, notification of protocol and/or consent form changes, adverse events, and termination of the study according to the appropriate IRB requirements. Risk Assessment

**Interviews and record reviews.** As with any study that involves collecting data, it is possible that someone who is not involved with the study may get access to participants' confidential information. Every precaution will be taken to secure participants' personal information to ensure confidentiality. At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms and in the study database instead of names and other private information. A separate list that links each participant's name to the study identification number will be maintained for future reference and communication.

### 8.3.2 Potential Benefits of Study Participation

Direct benefits: There are no direct benefit to the subjects.

Indirect benefits: Findings derived of this study will help increasing the understanding of the experience of living with DS and OSAS, and provide useful information for a future intervention trial of adherence to PAP in this population.

### 8.3.3 Risk-Benefit Assessment

The risks of this study are not greater than minimal risk.

## 8.4 Recruitment Strategy

CHOP participants will be recruited from the Sleep Center and the Down syndrome clinic, which are within the division of the investigators of the current proposal. Caregivers meeting eligibility criteria will receive a letter and a follow-up phone call from the investigators inviting them to participate in a one-time phone interview.

Cincinnati study participants will be identified for preliminary eligibility by study physicians and through the CCHMC DS clinic.

## 8.5 Informed Consent and HIPAA Authorization

A member of the study team at CHOP will be responsible for obtaining verbal informed consent from each participant. Informed consent will be obtained before this research study. Prospective participants will be given unlimited time to decide their participation. They will be asked to explain back to the investigators the nature of the study, study procedures and the risks and benefits of participation to assure their understanding.

A member of the study team at Cincinnati will obtain written consent for study procedures.

All aspects of the study will be explained in detail to each family by a team member. All questions will be answered and participants and families will be given time to consider their decision. They will be informed of the nature of this research, its potential benefits and possible risks. They will be informed that they are free to refuse participation or to withdraw from the study and that this will not affect any future medical care.

## 8.6 Payment to Subjects/Families

### 8.6.1 Payments to participants for time and inconvenience (i.e. compensation)

- Participants at CHOP will receive a $50.00 gift card for their participation.
- Participants at Cincinnati will receive a $50.00 reloadable debit card (ClinCard).

# 9 PUBLICATION

It is anticipated that the completed study will be submitted for publication to a peer-reviewed medical journal.

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