

Efficacy of Tympanostomy Tubes for Children with Recurrent Acute Otitis Media

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997)
- National Institutes of Health (NIH) Clinical Terms of Award
- Approved protocol

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
AE	Adverse Event
AOM	Acute Otitis Media
AOM-SOS	Acute Otitis Media-Severity of Symptoms Scale
CCP	Children's Community Pediatrics
CFR	Code of Federal Regulations
CHP of UPMC	Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center
CIQ	Caregiver Impact Questionnaire
CNMC	Children's National Medical Center
CO ₂	Carbon Dioxide
CRA	Clinical Research Associate
CRNP	Certified Registered Nurse Practitioner
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMSU	Data Management and Statistical Unit
DSMB	Data and Safety Monitoring Board
DxEAR	Diagnostic Ear Assessment Resource
eCRF	Electronic Case Report Form
ENT	Ear Nose and Throat
ePROM	Enhancing Proficiency in Otitis Media
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
<i>H. influenzae</i>	<i>Haemophilus influenzae</i>
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intent-to-treat
<i>M. catarrhalis</i>	<i>Moraxella catarrhalis</i>
MIC	Minimum Inhibitory Concentration
Micro Lab	Microbiology Laboratory
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCCLS	National Committee for Clinical Laboratory Standards
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NLM	National Library of Medicine
NP	Nasopharyngeal
OM-6	Otitis Media 6 Questionnaire
OME	Otitis Media with Effusion

PA	Pennsylvania
PCV-7	Pneumococcal Conjugate 7-valent vaccine
PCV-13	Pneumococcal Conjugate 13-valent vaccine
PDD	Protocol Defined Diarrhea
PE	Physical Examination
PittNet PBRN	Pediatric Practice Based Research Network
RN	Registered Nurse
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SOS	Severity of Symptoms
TT	Tympanostomy Tubes
TTP	Tympanostomy Tube Placement
TBD	To Be Determined
TM	Tympanic Membrane
US	United States

1 KEY ROLES

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Please refer to the protocol-specific communication plan in the Manual of Procedures (MOP) for other contact information.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

In 2006, the most recent year for which data are available, 667,000 US children under age 15 years underwent tympanostomy tube placement (TTP) for otitis media, making it the most frequently performed surgical procedure after the newborn period in this age group, and constituting more than 20% of all ambulatory surgeries in this age group.¹ Most of the operations were performed in children under 3 years of age.

Seventy percent of children experience at least one episode of acute otitis media (AOM) during the first year of life,^{2,3} and 93% by age 7.⁴ About 20% have recurrent AOM (rAOM), conventionally defined as ≥ 3 episodes in 6 months or ≥ 4 episodes in 12 months with at least 1 episode in the preceding 6 months. Efforts to reduce the rate of recurrence in such children have embodied two main approaches: low-dose antimicrobial prophylaxis or TTP. Studies of the efficacy of these approaches have been relatively few and have had various methodological limitations, particularly regarding ascertainment of previous AOM episodes and the stringency of criteria used for the diagnosis of AOM and for clinical trial eligibility. In these studies, prophylaxis has appeared effective in reducing by about half the number of AOM episodes in the succeeding 2 years, amounting to a reduction of about 0.5 to 1.5 episodes per child-year.⁵ However, prophylaxis seems no longer advisable because of concerns about its adverse effects and its contribution to the emergence of bacterial resistance.⁶ The efficacy of TTP for preventing rAOM, assumedly by maintaining middle-ear ventilation, remains unclear; limited evidence suggests short-term benefits similar in magnitude to those of antimicrobial prophylaxis.⁷ An advantage of TTP is that AOM in children with tubes can be treated with topical rather than systemic antibiotics, potentially minimizing adverse effects and contributions to bacterial resistance. Benefits of TTP, however, must be balanced against (1) risks of anesthesia, especially before age 3 years,⁸ and of the development, after surgery, of tube otorrhea, blockage of the tube or its premature extrusion or displacement into the middle ear cavity, and tympanic membrane (TM) scarring, retraction pocket, granulation tissue, or persistent perforation;⁹ and (2) cost. Although in recent years, there has been a noticeable decline in the overall number of TTP procedures,¹⁰ it seems plausible that this decline may result from a greater decline of TTP procedures among children with persistent middle-ear effusion that outweighs an increase in procedures among children with rAOM. A critical need thus exists on behalf of such children to establish TTP's risk/benefit ratio.

Review of Relevant Literature. The efficacy of TTP in preventing recurrences has been studied in four randomized, controlled trials of children referred to ENT because of history of rAOM.¹¹⁻¹⁴ In two trials some children also had persistent middle ear effusion (MEE) at entry.^{11,12} In one of these, *Gebhart et al.* randomized 108 children age <3 years to either TTP or observation, and followed them for 6 months. Among the 95 children for whom results were available, 54 children in the TTP group had 36 AOM episodes and 41 children in the observation group had 89 episodes (rate difference 1.3 vs. 4.3 episodes per child-year; $P<0.001$).¹² In the other trial, *Gonzalez et al.* randomized 63 children aged <4 years to either TTP, prophylaxis, or placebo, and followed them

for 6 months. Treatment failure was defined as ≥ 2 episodes of either AOM or otorrhea within 3 months. Five of 22 children in the TTP group failed, compared with 12 of 20 in the placebo group ($P=0.03$). During 6 months, 19 AOM episodes occurred among 22 children in the TT group, compared with 40 among the 20 children in the placebo group (rate difference 1.7 vs. 4.0 episodes per child-year; $P<0.01$).¹¹ Casselbrant *et al.* randomized 264 children 7 to 35 months of age free of MEE to either prophylaxis, TTP, or placebo, and followed them for 2 years. No significant difference was noted between children undergoing TTP and children receiving placebo in the average number of AOM episodes (rate difference 1.03 vs. 1.08 episodes per child-year; $P=0.25$). Persistent TM perforations developed in 4% of children in the TTP group.¹³ Kujala *et al.* randomly assigned 300 children aged 10 months to 2 years to either TTP, TTP plus adenoidectomy, or neither, and followed them for 12 months. The primary outcome was intervention failure, defined as ≥ 2 AOM episodes in 2 months, ≥ 3 in 6 months, or persistent MEE for 2 months. Failure occurred in 21 of 100 children in the TTP group (21%), 16 of 100 children in the TTP plus adenoidectomy group (16%), and 34 of 100 children in the control group (34%) (rate differences -13% [95% CI -25% to -1%] between the TTP group and the control group, $P=0.04$; and -18% [95% CI -30% to -6%] between the TTP plus adenoidectomy group and the control group, $P<0.01$). Reductions in the rate of AOM recurrences provided by surgery were modest: compared with the rate of 1.70 episodes per child-year in controls, the rate in children undergoing TTP was 1.15 (difference -0.55 [95% CI -0.93 to -0.17]), and the rate in children undergoing TTP plus adenoidectomy was -0.91 (difference -0.79 [95% CI -1.14 to -0.43]).¹⁴

A recent systematic review of TTP in children with rAOM concluded: “evidence of the effect of... insertion of TT is very limited. In light of the relatively small effect it seems ethical to carry out well-designed randomized studies with non-treatment control groups and relevant outcome measures as improvement in quality of life for children and the whole family, absence from day care, parents absent from work, and adverse effects.”⁷ In the present ear nose and throat (ENT) and pediatric practice paradigms, antimicrobial prophylaxis is no longer acceptable because assessment of the relative risk-benefit profiles has shifted given short- and long-term effects of injudicious antibiotic use.⁶ Because of the large numbers of young children in the U.S. who undergo TTP and the remaining uncertainties concerning the efficacy of TTP, we believe it is important to settle questions of benefit vs. risk and cost in definable subgroups of children.

Preliminary Studies

Investigator experience with large, long-term, randomized, controlled clinical trials.

Since the 1970s our research team has conducted large-scale, randomized, controlled trials evaluating procedures and treatments commonly used for frequently occurring pediatric conditions, and has followed successfully large cohorts of children for extended periods of time. These trials have included tonsillectomy for recurrent pharyngitis^{15,16} adenoidectomy for otitis media,^{17,18} TTP for persistent MEE,¹⁹ outpatient vs. inpatient antibiotics for acute pyelonephritis,²⁰ influenza vaccine for preventing AOM,²¹ prophylactic antimicrobials for children with vesicoureteral reflux,²² antimicrobials for AOM in children under age 2,²³ duration of therapy for AOM in children under age 2 (5 days vs. 10 days; in progress), and duration of therapy for urinary tract infection (5 days vs. 10 days; in progress). Many of these studies have involved multiple centers, and most have been supported by NIH. Particularly pertinent to the present

proposal are the trial that evaluated the efficacy of antimicrobials for AOM²³ and the ongoing trial evaluating duration of therapy for AOM, both with similar follow-up procedures.

Treatment of AOM in Children Under 2 Years of Age²³

291 children 6 to 23 months of age with AOM diagnosed stringently were randomly assigned to receive either amoxicillin–clavulanate or placebo for 10 days. Symptomatic response and treatment failure rates were measured. Among children who received amoxicillin–clavulanate, 35% had initial resolution of symptoms by day 2, 61% by day 4, and 80% by day 7; among children who received placebo, corresponding values were 28%, 54%, and 74%, respectively ($P=0.14$). For sustained resolution of symptoms, corresponding values were 20%, 41%, and 67% in the amoxicillin–clavulanate group, compared with 14%, 36%, and 53% in the placebo group ($P=0.04$). Mean symptom scores over 7 days were lower for children in the amoxicillin–clavulanate group than those in the placebo group ($P=0.02$). The rate of treatment failure (persistence of signs of acute infection) was lower for children treated with amoxicillin–clavulanate than for those receiving placebo: 4% vs. 23% at or before day 4 or 5 ($P<0.001$) and 16% vs. 51% at or before day 10 to 12 ($P<0.001$). Mastoiditis developed in one child who received placebo. Diarrhea and diaper dermatitis were more common among children who received amoxicillin–clavulanate. No significant changes in rates of nasopharyngeal (NP) colonization with nonsusceptible *S. pneumoniae* were noted.

Duration of Therapy for AOM in Children Under 2 Years of Age

We received a contract from NIAID (HHSN272201000047C) to study shortening the duration of therapy in young children with AOM as a strategy for reducing the likelihood of antimicrobial resistance. This is a Phase 2b multicenter, randomized, double-blind, placebo-controlled clinical trial comparing reduced-duration with standard-duration therapy in children aged 6 to 23 months with AOM. The trial will compare the efficacy of reduced-duration with standard-duration therapy for as many as three successive episodes of AOM, using for each child for each episode a consistent strategy entailing the same blinded therapy as assigned at entry. In the event that a child develops three episodes, [the third and] any subsequent episodes will be treated with amoxicillin-clavulanate for 10 days. Each child will be followed for an entire respiratory season (October through May). Final assessment for NP bacterial resistance will occur the following September (up to 1-year follow-up). The primary objective is to determine whether reduced-duration therapy (5 days of amoxicillin-clavulanate + 5 days of placebo) is non-inferior in efficacy to standard-duration therapy (10 days of amoxicillin-clavulanate) as determined by the proportion of children categorized as treatment failure by Day 12-14. Secondary objectives include determining whether a strategy of reduced-duration therapy results in decreased NP resistance, no increase in the number of recurrences, decreased antibiotic utilization, no increase in symptom burden (Days 6-14), equivalent treatment failure rates during recurrences, and an improved safety profile. Exploratory objectives will determine whether the reduced-duration therapy strategy results in no difference in utilization of healthcare resources and increased parental satisfaction with therapy. A total of 520 children were enrolled and will have completed follow-up by September 2015. Results are currently being analyzed.

Investigator contributions toward enhancing AOM diagnostic accuracy and increasing the stringency of AOM diagnostic criteria, and investigator efforts to increase precision of research outcomes

Drs. Hoberman, Paradise and Shaikh have devoted continuing effort to improving methods of teaching physicians accurate diagnosis of otitis media, particularly differentiating AOM from otitis media with effusion (OME), through publications²³⁻²⁶ and images obtained otoendoscopically. These programs have been presented at meetings of the Pediatric Academic Societies and the American Academy of Pediatrics (AAP), have been used at investigators' meetings for validating the skill of clinicians participating in research, and have been reviewed in journals.^{27,28} We have also developed two Videos in Clinical Medicine for the *N Eng J Med*, on pneumatic otoscopy and cerumen removal, and on diagnostic tympanocentesis.²⁹

Sponsored by the Centers for Disease Control and Prevention and the Association of American Medical Colleges, we developed a comprehensive educational curriculum for training in the diagnosis of AOM, which was implemented at 5 residency programs (<http://pedsed.pitt.edu>; ePROM, Enhancing Proficiency in the Diagnosis of Otitis Media).³⁰ At the 2009 Annual meeting of the Pediatric Academic Societies, Dr. Hoberman, as Chief of the Division of General Academic Pediatrics at Children's Hospital of Pittsburgh of UPMC (CHP of UPMC) received the Outstanding Teaching Award of the Academic Pediatric Association for the development of these educational programs. Dr. Hoberman served as a member of the AOM Management Guideline Subcommittee of the AAP and was responsible for the diagnostic section that endorsed the stringent criteria used in our recent trials.^{5,23}

To enhance the quality of observations in AOM clinical trials, Dr. Hoberman incorporated the diagnostic criteria previously described, together with TM images obtained otoendoscopically, into an electronic case report form (eCRF). Investigators complete this form and submit it to a central database, triggering an email that has permitted central review of all images obtained in recent multicenter AOM clinical trials we have conducted. This technology, recently endorsed in a Food and Drug Administration (FDA) guidance document for AOM clinical trials, has enabled clinicians at participating study sites to discuss otoscopic findings as needed with Dr. Hoberman, further enhancing the accuracy of AOM diagnoses that determine eligibility and primary outcome.

Development of rAOM severity/risk scale (rAOM-SRS)

Using previously reported demographic and clinical characteristics associated with increased likelihood of AOM recurrences, Drs. Hoberman and Paradise developed the rAOM-SRS to categorize children as either high-risk or low-risk. These categories will be used in secondary analyses of treatment efficacy. We assigned ratings of 0, 1, or 2 (shown in parentheses in Table 1) to each characteristic, based on previously reported strengths of associations and/or our clinical experiences. These clinical and demographic factors are operative singly or together throughout the child's prior history including the screening phase of the trial, at the time of randomization, and throughout the follow-up period. The factors comprise: (1) early age of onset of AOM;^{3,31} (2) number and frequency of previous episodes of AOM;³² (3) receipt of many courses of antibiotics and accordingly at higher risk of developing AOM caused by resistant pathogens;³³ (4) eligibility for randomization first having become evident during warm-weather

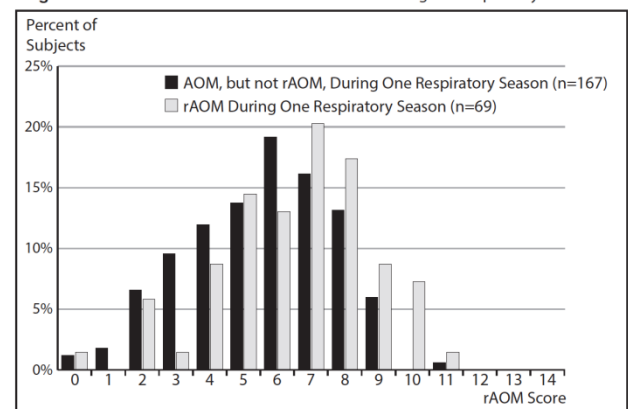
months, implying greater likelihood of being otitis-prone;³² (5) overall parental assessment of the severity of previous episodes of AOM;³¹ (6) eligibility for randomization despite not having been exposed to other young children;^{2,23} (7) extreme TM bulging with previous AOM episodes;²³ (8) usual bilaterality of previous AOM episodes;^{3,23} and (9) severity of symptoms.²³ Five of nine scale items relate to increased risk for rAOM; 4 items relate to average severity of recurrences. Exposure to other young children subsequent to randomization represents a particularly important risk factor; accordingly, we have included it as an independent stratification variable rather than in the composite rating. We obtained preliminary data on applying the score to 236 children enrolled in our duration-of-treatment study described previously (not the previously described amoxicillin-clavulanate vs. placebo study whose data contributed to our choice of characteristics of interest for the scale) in order to determine whether sufficient numbers of children would have been assigned to “high-risk” and “low-risk” groups to permit meaningful analyses. The only variable that retrospectively could not be assessed was #5, parental overall assessment of previous AOM episodes, due to concerns about recall bias. Accordingly, a total of 14 points could potentially be assigned (instead of 16) for the remaining 8 items. A total of 69 children met criteria for rAOM during their follow-up for one respiratory season (range 60-240 days); 55% had a total score ≥ 7 and 35% a score ≥ 8 . The Figure shows the proportions of children in relation to rAOM-SRS scores for 69 children with rAOM and 167 children who had AOM but did not meet rAOM criteria during one respiratory season. Consistently among children with rAOM-SRS scores ≥ 7 , the percentages of rAOM children were greater than the corresponding percentages of non-rAOM children, with the reverse being the case for children with scores ≤ 6 . The mean scores were 6.49 [2.26] vs. 5.54 [2.15] for rAOM and non-rAOM groups, respectively; $P=0.003$).

Table 1. rAOM Severity/Risk Scale (rAOM-SRS)

1	Age at 1 st AOM	≥ 6 mo (0)		<6 mo (1)
2	No. of previous episodes by history	3 in 6 mo or 4 in 1 yr (0)	4 in 6 mo or 5 in 1 yr (1)	≥ 5 in 6 mo or ≥ 6 in 1 yr (2)
3	No. of courses of antibiotic in preceding 6 mo	≤ 3 (0)		>3 (1)
4	Season at randomization	November-April (0)		May-October (2)
5	Parental overall assessment of previous AOM episodes	Mild (0)	Moderate (1)	Severe (2)
6	Exposure to other children during 6 months prior to randomization*	Not Exposed (0)		Exposed (2)
7	Usual TM bulging, based on medical records, and findings during screening and/or at randomization	Slight or unknown (0)	Moderate (1)	Marked (2)
8	Usual laterality based on history, and findings during screening and/or at randomization	Unilateral (0)	Mixed uni/bilateral (1)	Bilateral (2)
9	Average AOM-SOS score during screening and/or at randomization	≤ 6 (0)		>6 (2)

* Exposure is defined as exposure to 3 or more children for at least 10 hours per week.
Total ≤ 7 points – Nonsevere/low-risk rAOM
Total 8-16 points – Severe/high-risk rAOM

Figure. rAOM-SRS scores in 207 children followed during one respiratory season



Antimicrobial resistance trends in children with AOM

We have conducted studies of children with AOM for over 15 years, following trends in antimicrobial resistance and *Streptococcus pneumoniae* serotype prevalence as well as findings concerning other pathogens.^{21,23,34-36} In studies conducted before the introduction of 7-valent pneumococcal conjugate vaccine (PCV7), and up to and including the period following the introduction of 13-valent pneumococcal conjugate vaccine (PCV13), we reported that despite community-wide efforts to decrease inappropriate use of antibiotics, the relatively high prevalence in this community of *S. pneumoniae* isolates that are penicillin-nonsusceptible has remained essentially unchanged. We have observed considerable change in serotypes of *S. pneumoniae* recovered from children with AOM. Before routine vaccination in 1999-2000, serotypes observed were principally (59%) those included in PCV7; 25.5% were penicillin-nonsusceptible. By the mid-2000s, these serotypes had decreased in frequency while new serotypes, particularly 19A, emerged. In 2010, when PCV13 was introduced, carriage of PCV7 serotypes had been virtually eliminated (1.8%), and 19A had decreased substantially and been replaced by new serotypes. Predominant serotypes observed have been 15A/B/C (23.3%)--30% penicillin-nonsusceptible, followed by 35B (8.9%)--100% penicillin-nonsusceptible. The prevalence of levofloxacin resistance among *S. pneumoniae* isolates has been 1%. Table 3 below summarizes serotype distribution and susceptibility information from our previous and ongoing clinical trials, and illustrates the virtual disappearance of PCV7 serotypes, the subsequent decrease in PCV13 serotypes, and the more recent emergence of non-vaccine serotypes. Other studies have had similar findings.³⁷⁻⁴⁰

Our studies since 1999 showed that NP colonization with *Haemophilus influenzae* had an initial increase (41%) in 2003-2005 suggesting replacement of *S. pneumoniae* after

Table 3. Susceptibility and serotype distribution of *S. pneumoniae* isolates obtained from NP specimens in children 6-23 months diagnosed with AOM.

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	P
Years included in this study	1999-2000	2003-2005	2006-2009	2011-2013	
No. children in parent study	N=417	N=326	N=282	N=228	
No. children from parent study with NP at time of AOM	N=175	N=87	N=282	N=228	
No. (%) children with <i>S. pneumoniae</i> on NP at time of AOM	N=85 (48.6%)	N=33 (37.9%)	N=140 (49.6%)	N=113 (49.6%)	
PCV-7	49 (57.6%)	14 (42.4%)	7 (5.0%)	2 (1.8%)	<.001
PCV-13	17 (20.0%)	7 (21.2%)	56 (40.0%)	14 (12.4%)	<.001
Vaccine related	3 (3.5%)	0	14 (10.0%)	17 (15.0%)	.01
Non-Vaccine serotypes	16 (18.8%)	12 (36.4%)	63 (45.0%)	80 (70.8%)	<.001
Penicillin susceptible	60 (74.1%)	21 (63.6%)	88 (62.9%)	76 (67.3%)	.38
Penicillin non-susceptible	21 (25.9%)	12 (36.4%)	52 (37.1%)	37 (32.7%)	<.001
Parent study	Impact of influenza vaccine on AOM	NP surveillance post PCV7	Antibiotic vs. placebo for AOM	5 vs. 10 d of antibiotics for AOM (ongoing)	

Penicillin susceptible: minimum inhibitory concentration (MIC) <0.1 mcg/mL

Penicillin non-susceptible: minimum inhibitory concentration (MIC) ≥0.1 mcg/mL

introduction of PCV7; however, this was followed by a decrease in colonization in our most recent cohort (2012-2014). Currently, 29% of children 6-23 months of age with AOM are colonized with *H. influenzae*.⁴¹ Further, our recent data on 206 children support the findings that children with infrequent episodes of AOM and less systemic antibiotic exposure (n=146) are less likely to be colonized with resistant bacteria (7.5% non-susceptible *S. pneumoniae* or β -lactamase + *H. influenzae*) than otitis-prone children (n=60)(18.3%; $P=0.04$). Accordingly, we expect that children randomized to TTP will be exposed to less systemic antibiotic and will be

less likely to be colonized with resistant pathogens. These findings indicate continuing change and underscore the need for vigilance to inform vaccine development and clinical management.

Investigator experience in establishing collaboration with otolaryngologists in the design and implementation of various studies, including particularly clinical trials involving surgical vs. nonsurgical management; consistent, high-quality statistical support; and experience in communicating with and obtaining informed consent from families in order to obtain participation of their children in trials addressing treatments or procedures for which equipoise exists

Since the late 1960s we have developed cooperative working relationships in planning and executing large clinical studies in collaboration with otolaryngologists.^{9,16-19,42-44} These studies have included various clinical trials in which children were randomized to receive or not receive a specific surgical procedure (i.e. tonsillectomy, adenoidectomy, or TTP). All of these studies over the past 22 years have benefited from key participation in planning and co-responsibility for analysis by a single statistical team comprising Howard Rockette, PhD, Marcia Kurs-Lasky, MS, and more recently Jong-Hyeon Jeong, PhD, all of whom have particular expertise in analyzing specific outcomes in clinical trials. We have also recently studied reasons for parents' consenting or not consenting to allow their children to participate in clinical research studies.⁴⁵ In recognition for his research accomplishments, Dr. Hoberman received the Academic Pediatric Association 2014 Research Award. The award acknowledges the contribution of an individual in advancing pediatric knowledge through excellence in research, characterized by originality, creativity and methodological soundness.⁴⁶

2.2 Rationale

The rationale for this research is based on a belief that the limited nature of the benefit of TTP found in earlier clinical trials may have been the result of enrolling children whose previous illness episodes had not been diagnosed using stringent criteria and/or whose ascertainment of illness had relied on undocumented histories. In contrast, as in our recent clinical trial,²³ in our projected trial comparing TTP with nonsurgical management, clinicians will be trained otoscopists, all observations will be documented and supported with digital TM images obtained otoendoscopically (endorsed recently by the U.S. FDA, and we will use stringent AOM diagnostic criteria (endorsed recently in AAP guidelines⁵) coupled with stringent entry criteria and close follow-up.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

TTP carries with it the potential risks of anesthesia, especially before age 3 years, and of the development, following surgery, of tube otorrhea, blockage of the tube, or its premature extrusion or displacement into the middle ear. Possible TM sequelae include scarring, retraction pocket, granulation tissue, and persistent perforation. Finally, the cost of TTP is substantial. By avoiding overuse should TTP prove to have limited effectiveness, fewer young children will be exposed to

general anesthesia, long-term TM sequelae, and health care expenditures may be lessened. The primary risk of participation in the study for children randomized to nonsurgical management would be the potential for developing rAOM that would be treated with systemic antimicrobials (as opposed to topical antibiotics) with a resulting increase in certain adverse events (principally diarrhea and yeast infections), and the potential for encouraging the emergence of bacterial resistance. An important potential benefit of this study, should TTP prove to be quite efficacious, consists of the possibility that fewer children may develop NP colonization with resistant bacteria, with correspondingly fewer day care and adult/elderly household contacts becoming colonized, thus reducing the risk of their developing invasive or noninvasive pneumococcal disease. Under such conditions, the risk of impairment of overall child/family function might be lessened.

Parents will be informed of these possibilities, and advised that no definitive standard of care exists, particularly in light of the increasing trend toward sharp reductions in the use of prophylactic antimicrobials because of concerns about the emergence of bacterial resistance. They will be advised in the informed consent document that TTP is widely accepted by physicians in the US, but not necessarily in other countries where a lack of consensus exists regarding the advisability of TTP for rAOM. As noted below, the investigators will follow study participants closely after initiating therapy for an AOM episode, and with follow-up visits scheduled every 8 weeks. We will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM.

2.3.2 Adequacy of protection against risk

Recruitment and Informed Consent

All key personnel and research staff have completed the required training and certification for research integrity, protection of human subjects, research with children, HIPAA privacy, and blood-borne pathogens. Children for this study will be recruited from several pediatric general practice locations into a screening phase and will have to meet all inclusion and exclusion criteria before actual enrollment into the randomized phase of the study. In the screening phase, we will obtain informed consent from the parent(s) of children who are felt to be at risk for rAOM, and follow them prospectively. In order to document the occurrence a minimum of one episodes of AOM during the screening phase, children will be followed closely and examined by our study team. We will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM. This will be required in order for subjects to move to the randomization phase. Once the study has been explained, all questions have been answered, and informed consent has been obtained, eligible subjects will undergo central randomization within strata based on age (6-11 months, 12-23 months and 24-35 months) and degree/history of exposure to other children (exposed, or not exposed to ≥ 3 children for ≥ 10 hours/week).

Treatment Group A: TTP

Treatment Group B: Nonsurgical management

Randomization information will be programmed into the eCRF and study personnel will schedule, within 2 weeks, TTP for children who are assigned to treatment group A. No attempt will be made to blind treatment assignment.

Protection against risk

Study investigators will be available through a cellular phone (412) 999-EARS 24 hours a day, 7 days a week for children enrolled in the study. Parents will be asked about their child's overall clinical status and children will be seen within 48 hours (usually on the same day) or referred to the Emergency Department (ED) if deemed appropriate.

All paper records containing identifying information will be kept in locked files accessible only to study staff and unlocked only while a study staff member is working with the files. Information regarding individual subjects will be kept private and shared only with the IRB and appropriate government agencies. Primary care providers will be informed about their patient's progress periodically and will be notified if problems in management occur as detailed above.

2.3.3 Potential benefits of the proposed research to the subjects and others

Study subjects may benefit from early detection and appropriate antibiotic treatment (topical or systemic) of recurrences of AOM. This investigation will provide indirect benefit to children who experience rAOM because analysis of these carefully collected data will be instructive in determining whether children with rAOM should generally be treated with TTP.

2.3.4 Importance of the knowledge to be gained

This contribution is important because it will provide clinicians and parents the necessary evidence to determine whether TTP, as compared with nonsurgical management, results in a reduction in the number of children's AOM recurrences over time, and accordingly supports the rationale for the most frequently performed surgical procedure in young US children. If TTP proves effective and as a result is used more widely, fewer children may exhibit NP colonization with resistant bacteria, and correspondingly fewer adult/elderly household contacts may become colonized, thus decreasing their risk of developing respiratory disease, and invasive pneumococcal disease in particular. On the other hand, should TTP prove not substantially effective and reductions in the number of procedures result, fewer young children will be exposed to general anesthesia, and fewer will develop short-term complications of TTP and/or long-term TM and possibly auditory sequelae. Under those circumstances, health care expenditures would be reduced as well. However, irrespective of the surgical-vs-nonsurgical results, their application may be expected to result in improved overall child/family functional status.

The management of children with rAOM has long been controversial. Efforts to reduce the rate of recurrence have taken two approaches: antimicrobial prophylaxis and TTP. Studies evaluating these approaches have been characterized by methodological limitations, particularly in the ascertainment of previous AOM episodes and in the stringency of AOM diagnostic criteria. Further, since antimicrobial prophylaxis seems no longer advisable because of concerns about

adverse events and about its contribution to the emergence of bacterial resistance, TTP has become a frequently used therapeutic option despite the absence of solid evidence supporting its widespread use. A properly designed randomized clinical trial, with stringent AOM diagnostic criteria, to determine both eligibility and outcome, in which all observations will be documented and supported with digital TM images obtained otoendoscopically (as endorsed by the US FDA), together with follow-up for a clinically meaningful 2-year period, will enable us to achieve the specific aims of this study, and to provide support for, or call into question this frequently performed surgical procedure in children. The proposed investigation is designed to overcome the limitations of previous studies and to address this important public health question. Risks to participants are outweighed by the potential gains to the children enrolled, and to the many other children with rAOM. The stringent safeguards built into the proposal for the early detection and treatment of clinical failures and recurrences of rAOM will also help protect study participants. Such surveillance would likely not be available outside a study setting.

3 OBJECTIVES

3.1 Study Objectives

The present proposal is a Phase 3, multicenter, randomized, clinical trial among children aged 6-35 months with rAOM. Its goal is to determine whether TTP as compared with nonsurgical management will meaningfully improve the children's AOM experience over the succeeding 2 years. A total of 240 children diagnosed with rAOM will be enrolled at participating clinical study sites, namely, CHP of UPMC, Pittsburgh, PA and its affiliated Pediatric PittNet Practice-Based Research Network; and Children's National Medical Center (CNMC), Washington, DC and its affiliated Children's Pediatricians and Associates Practices (CP&A), and KPAR (Kentucky Pediatric/Adult Research) in Bardstown, KY,. Participating clinical study sites will enroll approximately 100 eligible children per year over a period of 2.5 years; children will be followed for a 2-year period. Children recruited from the target population will reflect the community at large at each participating site, encompassing urban (CHP and CNMC), suburban, and rural (Pediatric PittNet and CNMC-affiliated practices) populations, to enhance the generalizability of study findings and encourage the translation of study findings to clinical practice.

Primary Objective:

To determine the efficacy of TTP in children aged 6 to 35 months, the age group in whom rAOM is most troublesome. This objective is in keeping with our *long-term goal* of evaluating frequently performed pediatric treatments and procedures that entail substantial use of health care resources but whose value has not been adequately substantiated.^{16, 17, 19, 20, 23, 47-49} Our *central hypothesis* here is that in children with rAOM who have conventional indications for TTP, the operation will prove effective in reducing morbidity from AOM over the ensuing 2 years overall, but that the benefit in a more severely affected, and therefore higher-risk subgroup may be substantially greater than in a less severely affected subgroup, in whom benefits of TTP may not outweigh risks. We will test our *central hypothesis* by pursuing, in children with rAOM, the following *specific aim*

To determine the extent to which TTP reduces the rate of AOM recurrences over a 2-year period.

Hypothesis: TTP will reduce the rate overall. Secondarily, higher-risk children will experience greater benefit than those at lower risk who will have fewer recurrences and for whom benefits may not outweigh risks.

Secondary Objectives:

To determine whether TTP as compared with nonsurgical management results in:

- Reduced antibiotic resistance of nasopharyngeal pathogens
- Greater cost-effectiveness in children at higher-risk for rAOM than in children at lower-risk. This will include determination of direct medical and non-medical costs, determination of effectiveness by tracking days with either AOM symptoms and intact

TMs or tube otorrhea, and medication-related adverse events or complications. Secondary cost-effectiveness outcomes will determine how TTP for rAOM affects functional outcomes as measured by the OM-6 survey questionnaire and the Caregiver Impact Questionnaire (CIQ), to be described later.

- A lower proportion of children categorized as having treatment failure (defined below)
- Less severe AOM episodes, using both the *AAP definition* (severe, indicated by moderate or severe otalgia or temperature $>39^{\circ}\text{C}$)⁵ and by the *Acute Otitis Media-Severity of Symptoms (AOM-SOS)*³⁰ score on Day 1 of AOM recurrences
- A lower frequency of AOM recurrences
- Longer time-to-first AOM recurrence
- A differential proportion of AOM recurrences presenting with, respectively, intact bulging TM or tube otorrhea
- Fewer days per year on which subjects receive systemic antimicrobials for AOM
- Lower proportions and duration of selected adverse events during periods of antimicrobial therapy for AOM (protocol defined diarrhea [PDD, defined as the occurrence of ≥ 3 watery stools on 1 day or ≥ 2 watery stools on each of 2 consecutive days], diaper rash necessitating administration of topical antifungal therapy, and otorrhea)

The primary endpoint is the average number of AOM episodes during the 2-year follow-up period; we will compare mean rates of AOM recurrence between treatment groups. Secondary endpoints include the development of antimicrobial resistance among nasopharyngeal pathogens; direct medical and non-medical costs, proportion of children categorized as treatment failure (defined below), days with either AOM symptoms and intact TM or tube otorrhea, medication adverse events/complications, and functional outcomes for cost-effectiveness analyses; proportions of severe vs. non-severe AOM episodes; days to first AOM recurrence; total number of days children received antibiotics; and the occurrence of PDD up to Day 16, diaper dermatitis resulting in the prescription of an antifungal cream, and otorrhea.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the average number of AOM episodes during the 2-year follow-up period. Children enrolled in the study will be evaluated every 8 (± 1) weeks and at any time parent(s) or legal guardian(s) suspect the occurrence of AOM. If a subject is evaluated at a non-participating clinical site, parents will be asked to bring the subject to a study site for further evaluation. Findings of AOM will be counted as a recurrence if they have persisted or recurred ≥ 17 days after start of treatment for a preceding episode, because: (1) new episodes will have been treated with an antimicrobial for 10 days, and (2) most AOM episodes occurring ≥ 7 days

after completion of therapy are new infections with different pathogens rather than bacteriologic relapses (in one study, 59%, 74%, 86%, and 90% of infections occurring during the 1st, 2nd, 3rd and 4th week after therapy, respectively, were new).⁵⁰

Treatment failure. Children will be deemed to have experienced treatment failure if they develop at any time any of the following:

- a. 2 AOM recurrences within 3 months, 3 AOM recurrences within 6 months, or 4 AOM recurrences within 12 months
- b. ≥3 severe AOM recurrences within 12 months, with “severe” defined as showing either:
 1. Moderate or severe otalgia or temperature >39°C
 2. AOM-SOS score >6 on Day 1
- c. Persistent MEE for ≥12 successive months
- d. Otorrhea for ≥45 days cumulatively within a 12-month period
- e. TM perforation for ≥90 days following extrusion of TT
- f. PDD (associated with antimicrobial therapy for AOM) for ≥30 days cumulatively within a 12-month period, or treatment with intravenous fluids for PDD (associated with antimicrobial therapy for AOM) on ≥2 occasions
- g. Performance of TTP in children assigned originally to the nonsurgical treatment group
- h. Hospitalization for any otitis media-related reason, e.g. (1) unplanned admission overnight after surgery that was originally planned as ambulatory; (2) mastoiditis; (3) persistent otorrhea caused by pathogens resistant to oral antimicrobials; and (4) PDD (associated with antimicrobial therapy for AOM) severe enough to require hospitalization.
- i. Anesthesia reactions, to include laryngospasm, anaphylaxis, or a need for cardiopulmonary resuscitation during surgery;
- j. Receipt of ≥45 days cumulatively of systemic antimicrobials for AOM within a 12-month period

Secondarily, estimates of the difference in number of AOM episodes during a 2-year period between the TTP and nonsurgical groups in the higher-risk and lower-risk children, respectively, will be useful in determining whether TTP is more beneficial for the subgroup of children at higher risk. The precision of these estimates will depend on the proportion of children assigned to the higher-risk subgroup, as well as on the average number of episodes occurring in each risk subgroup.

Treatment of AOM episodes. Otorrhea occurring in children with TT in place will be considered indicative of acute infection, and in such instances a specimen of the discharge for standard microbiologic assessment will be obtained, when possible from the tube orifice directly. Such children will be treated with topical ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the affected ear twice daily for 10 days. Persistence of otorrhea after 7 days of treatment will be considered inadequate response, and children so affected will be prescribed empiric amoxicillin-clavulanate (90/6.4 mg/kg/day in two divided doses) followed by culture-directed therapy 48 hours later. Children randomized to nonsurgical management will receive stepwise therapy with amoxicillin-clavulanate (90/6.4 mg/kg in two divided doses for 10 days), and in the event of inadequate response, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the

AAP guidelines.⁵

3.2.2 Secondary Endpoints

- Secondary endpoints concerning bacterial resistance include (1) proportions of children whose NP cultures at randomization are, respectively, either negative for *S. pneumoniae* and *H. influenzae*, or positive for penicillin-susceptible pathogens, or positive for one or more penicillin-nonsusceptible pathogens, who subsequently are found on a follow-up NP culture to harbor one or more penicillin-nonsusceptible pathogens; (2) proportion of interim, non-illness visits at which a penicillin-nonsusceptible pathogen is recovered; and (3) for all AOM episodes, the proportions of *S. pneumoniae* and *H. influenzae* isolates recovered at a visit during April or May (end of the respiratory season) that are penicillin nonsusceptible. To enable these analyses we will obtain, at randomization and every 16 weeks thereafter, an NP culture in children aged 6 to 23 months and a throat culture in children aged ≥ 24 months. An incidental by-product of these analyses will be information as to whether the *S. pneumoniae* serotypes found are components of PCV13.
- Relative cost-effectiveness in children at higher risk for rAOM as compared with children at lower risk will include determination of direct medical and non-medical costs, determination of effectiveness by tracking days with either AOM symptoms and intact TMs or tube otorrhea, and medication-related adverse events or complications. Secondary cost-effectiveness outcomes will determine how TTP for rAOM affects functional outcomes as measured by the OM-6 survey questionnaire and the CIQ.

Determination of direct medical costs. Direct medical costs include costs of visits to healthcare providers and cost of medications, and will be ascertained from parent reports and medical records. At study visits every 8 weeks, we will ask parents about number/type of encounters with healthcare providers (ED, hospitalizations, surgeries, ENT, primary care provider) and about antibiotic use. Cost of research-only visits will not be included, except when parents state that it prevented a visit for an AOM-related concern. We will also review medical records to ensure that all visits have been captured. We will separate costs into those related and unrelated to AOM and its treatment. A clinician, masked to treatment assignment, will make this determination. This will allow us to compare both overall costs and costs specific to AOM between the two treatment groups.

We will use a social approach to measuring direct medical costs, and use information on the Medicare relative-value physician fee system from the Center for Medicare and Medicaid Services database to assign costs to physician services. We will take into account information from study records and medical records to assign a Healthcare Common Procedure Coding System (HCPCS) code to each visit. For primary care and ED visits, we will assume a level-3 service (HCPCS codes 99213 and 99283, respectively), and will use the HCPCS code (69436) to calculate cost of TTP—including a routine postoperative visit to the surgeon at 1 month. For the 12-month follow-up visit with the surgeon we will use the HCPCS code (99213). The number of visits will be multiplied by the unit cost of each visit. We will estimate costs of hospitalizations and ED visits by dividing charges for those visits

by the hospital's cost-to-charge ratio. The number of courses of medications used will be multiplied by the unit cost of each medication using the Red Book™ Drug reference book.

Determination of direct non-medical costs. At study visits, we will collect information on indirect costs of medical care associated with AOM, including travel expenses for visits, alternate daycare expenses for siblings, as well as time costs (e.g., time for missed work).

Determination of effectiveness. We will track days with (1) AOM symptoms with intact TMs, (2) tube otorrhea, and (3) medication-related adverse events or complications, by instructing parents to visit the study office when events are noted. The AOM-SOS scale will be administered at each visit. We will contact parents on Days 1-5 to determine whether symptoms on the AOM-SOS have resolved (score of 0 on all 5 items on Day 5), and ask parents to provide us with an end date. We will also contact parents on Day 12 (+/-2 days) to track symptoms that may not have resolved by Day 5. We will also track the occurrence of adverse events (PDD, diaper rash, otorrhea). To calculate quality adjusted life years (QALYs) for each arm, we will multiply the number of days with each outcome by the utility of that outcome. The first step will be to determine differences in costs and differences in effectiveness between the groups. We will use previously reported utility values.⁵¹

Functional outcomes. We will use the validated OM-6 survey questionnaire,⁵² and CIQ to assess the impact of rAOM on children and their caregivers.⁵³ The questionnaires will be administered at randomization and subsequently every 16 weeks (either in person or via phone interviews) during follow-up. The primary caregiver will complete these questionnaires. If the same caregiver is not present at each follow-up visit, the caregiver who initially completed the form will be called to gather the survey data over the phone for that time point. These will not be used as the primary measure because they cannot be easily translated into QALYs.

- Proportion of children categorized as treatment failure
- Severity of AOM episodes, using both the *AAP definition* (severe, indicated by moderate or severe otalgia or body temperature >39°C),⁵ and the *AOM-SOS scores* on Day 1 of AOM recurrences^{54,55}
- Frequency distribution of AOM recurrences
- Time-to-first AOM recurrence
- Proportion of AOM recurrences presenting with, respectively, intact bulging TM or tube otorrhea
- Total days per year subjects receive systemic antimicrobials for AOM
- During periods of antimicrobial therapy for AOM, (1) proportion of children with PDD, which will be defined as the occurrence of ≥3 watery stools on 1 day or ≥2 watery stools on each of 2 consecutive days, (2) diaper rash necessitating administration of topical antifungal therapy, and (3) otorrhea.
- Mean parental/legal guardian level of satisfaction with therapy.

Parental/legal guardian level of satisfaction with the assigned study intervention will be compared between the two treatment groups using a one-item global assessment. Parents will be asked to rate their level of satisfaction with the child's study medication at the end-of therapy (Day 12-14) using a 5-point scale (very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied and very satisfied).

4 STUDY DESIGN

This is a Phase 3, multicenter, randomized, clinical trial in children aged 6-35 months with rAOM. Its goal is to determine whether TTP compared with nonsurgical management will meaningfully improve the children's AOM experience over the succeeding 2 years. A total of 240 children diagnosed with rAOM will be enrolled at participating clinical study sites, namely, CHP of UPMC, Pittsburgh, PA; its affiliated Pediatric PittNet Practice-Based Research Network; CNMC, Washington, DC; and its affiliated CP&A, and KPAR (Kentucky Pediatric/Adult Research) in Bardstown, KY,. Participating clinical study sites will enroll approximately 100 eligible children per year over a period of 2.5 years; children will be followed for a 2-year period. Children recruited from the target population will reflect the community at large at each participating site, encompassing urban (CHP and CNMC), suburban, and rural (Pediatric PittNet and CP&A) populations, to enhance generalizability of study findings and encourage the translation of study findings to clinical practice.

Screening phase. Providers will refer potential subjects to the study who are thought to have had excessive numbers of episodes of AOM. There will be two phases of study participation. In the first, *screening phase*, we will obtain informed consent from the parent(s) of children who are felt to be at risk for rAOM, and follow them prospectively during a screening period. These children constitute ~20-25% of the numbers of children we have enrolled in the placebo-controlled study or the duration of treatment study. In this phase, our study team will We will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM. This will allow us to document a minimum of *one episode of AOM* as evidence that the parent's history of ≥ 3 AOM episodes in 6 months or ≥ 4 episodes in 12 months, as required for entry into the randomized phase of the study, is reasonably accurate. Episodes of AOM during the screening phase of the study will receive stepwise therapy with amoxicillin (90 mg/kg in two divided doses for 10 days), followed by amoxicillin-clavulanate (90/6.4 mg/kg in two divided doses for 10 days), and if the response remains inadequate, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the AAP guidelines.⁵

Definition of AOM. AOM will be defined in two ways: (1) acute symptoms accompanied by the presence of middle-ear effusion and moderate or marked TM bulging, or slight bulging accompanied by either otalgia or marked TM erythema; or (2) acute symptoms associated with rupture of the TM with purulent otorrhea. For episodes evaluated by study personnel, acute symptom(s) will be defined as a score ≥ 2 on the AOM-SOS scale (version 4.0). For episodes managed by other providers, the definition of AOM will require documentation in the medical record of both acute symptom[s] and either TM bulging or perforation of the TM with otorrhea. Observation of one AOM episode by study personnel will be required for subjects to move to the second, *randomization phase*.

Randomization phase.

Eligibility criteria. Children will be eligible to participate in the study if they (1) are aged 6-35 months, (2) have rAOM, defined as the occurrence of ≥ 3 AOM episodes in 6 months or ≥ 4

episodes in 12 months with ≥ 1 episode in the preceding 6 months, and (3) 1 of these AOM episodes have been documented by trained study personnel. We have developed a multimedia training protocol for newly-hired study clinicians (nurse practitioners and physicians).^{23,26,30} Our eCRF will permit capture of digital images obtained otoendoscopically, and will enable study clinicians at participating study sites to discuss otoscopic findings as needed with Co-PIs via computer or cellular phone, reinforcing the validity of AOM diagnoses that determine final eligibility.

Exclusion criteria. Children will be excluded if they (1) have a history of TTP, (2) have a chronic illness (e.g., cystic fibrosis, neoplasm, juvenile diabetes, renal or hepatic insufficiency, immune dysfunction, malabsorption, inflammatory bowel disease), (3) have a congenital anomaly that might increase the risk of recurrences (e.g., cleft palate, Down's syndrome), (4) have had bilateral OME for at least 3 months in addition to rAOM, or (5) have sensorineural hearing loss, (6) history of adenoidectomy surgery.

Randomization and treatment assignment. Once the study has been explained, all questions have been answered, and informed consent has been given, eligible subjects will undergo central randomization within strata based on age (6-11 months, 12-23 months and 24-35 months) and degree/history of exposure to other children (non-exposed vs. exposed to ≥ 3 children ≥ 10 hours/week). Children will be assigned in a 1:1 ratio to either undergo TTP or to be managed nonsurgically with antimicrobial treatment of individual episodes as they occur. Randomization information will be programmed into the eCRF so that study personnel will be able to schedule TTP with any of 3-4 ENT surgeons at CHP, CNMC, or KY, within 2 weeks. TT will be inserted under general anesthesia, using a small radial incision in the anteroinferior portion of the TM; a Teflon® Armstrong-type tympanostomy tube will be used. All children undergoing TTP will be treated with ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the external auditory canal twice daily for 3 days.

Follow-up. Children enrolled in the study will be evaluated every 8 (± 1) weeks. We will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM. AOM will be defined as previously detailed in the screening phase (4. Study Design. Screening Phase. Definition of AOM.) In addition, for ears with TTs in place, the occurrence of otorrhea, except in the immediate postoperative period, will be considered indicative of acute infection provided that the otorrhea is accompanied by acute symptom(s). In such children a specimen for culture will be obtained. If a subject is evaluated at a non-participating clinical site and diagnosed with AOM, parents will be asked to bring the subject to a study site for further evaluation. Each study visit will include a review of adverse events, utilization of health care and related resources, and receipt of concomitant medications since the preceding visit. At each visit a targeted physical examination including pneumatic otoscopy will be conducted. If AOM is diagnosed, a digital TM image will be obtained otoendoscopically; digital images of TMs considered normal will also be obtained periodically. An NP culture will be obtained at every other visit, or about 3 times per year. Also at every other visit, parents will be asked to document indicators of functional status (see Aim 3). To determine the impact of study-related monitoring on health care utilization, at the end of each routine study-related visit, parents will be asked

whether the visit either had no influence on scheduling, or prevented a primary-care provider visit, or induced a primary-care provider visit. At the end-of-study visit, parents will be asked to rate their level of satisfaction with the child's assigned medication using a 5-point scale (very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied and very satisfied).

Findings of AOM will be counted as a recurrence if they have persisted or recurred ≥ 17 days after start of treatment for a preceding episode, because: (1) we will treat new episodes with an antimicrobial for 10 days, and (2) most AOM episodes occurring ≥ 7 days after completion of therapy are new infections with different pathogens rather than bacteriologic relapses (in one study, 59%, 74%, 86%, and 90% of infections occurring during the 1st, 2nd, 3rd and 4th week after therapy, respectively, were new).⁵⁰ If a TT becomes obstructed, we will follow a standardized protocol that includes ofloxacin (5 drops twice daily for 14 days), followed by careful suction in clinic. In previous studies, Armstrong tubes remained in place for 12-18 months, allowing us to use an intention-to-treat approach for the majority of the follow-up period.^{44,56} As per standard practice, once TTs are extruded they will not be automatically replaced. However, if a TT becomes extruded within 6 months, it will be reinserted only if the child develops ≥ 2 episodes of AOM within 3 months. Beyond 6 months, a TT will be reinserted if the child meets criteria for rAOM (3 AOM episodes in 6 months, 4 AOM episodes in 12 months).

Treatment of AOM episodes. Otorrhea occurring in children with a TT in place will be considered indicative of acute infection, and in such instances a specimen of the discharge for standard microbiologic assessment will be obtained, when possible from the tube orifice directly. Such children will be treated with topical ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the affected ear twice daily for 10 days. Persistence of otorrhea after 7 days of treatment will be considered inadequate response, and children so affected will be prescribed empiric amoxicillin-clavulanate (90/6.4 mg/kg/day in two divided doses) followed by culture-directed therapy 48 hours later. Children randomized to nonsurgical management will receive stepwise therapy with amoxicillin-clavulanate (90/6.4 mg/kg in two divided doses for 10 days), and in the event of inadequate response, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the AAP guidelines.⁵

Adverse events. Parents will record information regarding the frequency and consistency of bowel movements in a diary in order to document the occurrence of PDD, defined as the occurrence of ≥ 3 watery stools in 1 day or ≥ 2 watery stools per day in 2 consecutive days, diaper rash necessitating administration of topical antifungal therapy, and otorrhea.

A Data and Safety Monitoring Board (DSMB) composed of outside experts regarding otitis media and randomized clinical trials, and a biostatistician, will be constituted. An Independent Safety Monitor (ISM) for Pittsburgh, PA, one for Washington, DC and one for Bardstown, KY, who are physicians at the respective study sites will be primarily responsible to provide independent safety monitoring in a timely fashion. Each ISM will be in communication with the PI at the participating clinical study site, the Medical Monitor, and the DSMB chair for any event that needs further evaluation. Reports generated for each event that summarize the status of the child will be reviewed by the ISM, the Medical Monitor, and the DSMB chair according to the

DSMB charter.

Data for this study will be reviewed by the DSMB per the DSMB charter. Trial review issues may include: study progress, including an assessment of data quality; outcomes; and adverse events/serious adverse events (AE/SAE) data, including out-of-range laboratory results; any pertinent new information; study procedures designed to protect the privacy of the subjects and the confidentiality of the data; interim analysis and final conclusions evaluating benefit-to-risk ratio of study participation. The DSMB may review applicable study data that include but are not limited to enrollment, demographics; efficacy outcomes; laboratory and safety data which may include AE/SAEs; concomitant medications; memory aid data; laboratory results (NP swab specimen cultures); TM images, otoscopic findings; and any physical examination findings. The DSMB will meet prior to initiation of the study, every 6 months thereafter, and after 120 children have completed the study (interim analysis). As an outcome of each review and meeting, the DSMB will make a recommendation to NIDCD at that time as to the advisability to continue, modify, or terminate the study.

5 STUDY ENROLLMENT AND WITHDRAWAL

A total of 240 eligible children 6 to 35 months of age (inclusive) with rAOM will be enrolled in the randomized trial over 2.5 years to determine whether TTP compared with nonsurgical management will meaningfully improve the children's AOM experience over the succeeding 2 years. Children will be recruited from primary care practices in 5 separate geographic regions, Western PA, Washington, DC, and Bardstown, KY representing urban, suburban and rural demographics. Subjects will be required to meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

Anticipated Challenges Associated with Subject Recruitment and Retention

The proposed clinical trial requires a period of participation of more than 2 years for each subject. We have conducted similarly long-term trials and will implement the same methods of subject recruitment and retention. These include frequent meetings with practitioners at clinical sites, immediate availability of investigators via cell phone, immediate availability of research personnel at enrollment sites, electronic monitoring of subject schedules, and PittNet teleconferences, webinars, and meetings. The proposed study procedures present only minor hardship, pain, or risk to participants, principally from ear examinations and performance of NP cultures. TTP carries the additional risks of general anesthesia and of long-term TM sequelae, although these must be addressed also when children are undergoing TTP outside of research settings and as part of their general medical care. Our recruitment methods in previous studies have resulted in the enrollment of larger numbers of subjects than will be required for the present study. Accordingly, major obstacles to recruitment or retention are not anticipated. A strategy to minimize parental inconvenience and to maximize recruitment and retention involves conducting all study-related visits at the various PittNet and CP&A study sites as well as at the Primary Care Center of CHP, Goldberg Children's Health Center at CNMC, and KPAR,. Parents will be reimbursed at each visit for their time and expenses, according to the local standards and IRB approval. As needed, taxicabs or other methods will be used to facilitate transportation. Finally, parents/legal guardians will be provided with a dedicated cell phone number, whereby investigators will be available to answer any concerns or questions parents/legal guardians might have. Screening logs of eligible and enrolled subjects will be maintained to detect the possibility of selection bias.

5.1 Eligibility Criteria

Children will be eligible to participate in the study if they (1) are aged 6-35 months, (2) have rAOM, defined as the occurrence of ≥ 3 AOM episodes in 6 months or ≥ 4 episodes in 12 months with ≥ 1 episode in the preceding 6 months, and (3) 1 of these AOM episodes have been documented by trained study personnel.

5.2 Exclusion Criteria

Children will be excluded if they (1) have a history of TTP; (2) have a chronic illness (e.g., cystic fibrosis, neoplasm, juvenile diabetes, renal or hepatic insufficiency, immune dysfunction, malabsorption, inflammatory bowel disease; (3) have a congenital anomaly that might increase the risk of recurrences (e.g., cleft palate, Down's syndrome); (4) have had bilateral OME for at least 3 months in addition to rAOM; (5) have sensorineural hearing loss and (6) history of adenoidectomy surgery.

5.3 Treatment Assignment Procedures

Children aged 6-35 months who meet inclusion criteria for rAOM will be eligible to participate in the second, *randomization phase* of the study.

5.3.1 Randomization Procedures

Randomization and treatment assignment. Once the study has been explained, all questions have been answered, and informed consent has been given, eligible subjects will undergo central randomization within strata based on age (6-11 months, 12-23 months and 24-35 months) and degree/history of exposure to other children (non-exposed vs. exposed to >3 children >10 hours/week). Children will be assigned in a 1:1 ratio to either undergo TTP or to be managed nonsurgically. Randomization information will be programmed into the eCRF so that study personnel will be able to schedule TTP with any of 3-4 ENT surgeons at CHP, CNMC, KY, Rochester or WVU within 2 weeks. TTs will be inserted under general anesthesia, using a small radial incision in the anteroinferior portion of the TM; a Teflon® Armstrong-type tympanostomy tube will be used. All children undergoing TTP will be treated with ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the external auditory canal twice daily for 3 days.

Eligible subjects will be enrolled at each of the participating clinical study sites as they present for enrollment, stratified within that site by age group and degree/history of exposure to other children, and randomly assigned in blocks within the respective stratum to 1 of the 2 treatment groups. Thus, while there will certainly be differences in the numbers of enrolled subjects between, for example, the various participating clinical study sites, the scheme we are proposing has a high probability of achieving close overall balance between the two treatment groups unless the average number of subjects per stratum is small.

Per International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating clinical study site to document the reason why an individual was screened but failed trial entry criteria. The reasons why individuals failed screening will be recorded on the screening log.

5.3.2 Masking Procedures

Because of the nature of treatment groups, study personnel and parents of study subjects will

not be blinded to treatment assignment.

5.3.3 Reasons for Withdrawal

The following events are to be considered sufficient reason for discontinuation of a subject from the study:

1. Any clinical AE, laboratory abnormality, intercurrent illness, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject.
2. Parent/legal guardian request; subjects are free to withdraw from participating in the study at any time upon request.

5.3.4 Handling of Withdrawals

Subjects who withdraw from the study after randomization will not be replaced. All subjects who were randomized will be included in the intent-to-treat analysis

Subjects who are categorized as experiencing treatment failure or are withdrawn will be asked to return for scheduled study visits including follow-up for safety and study endpoints.

If a parent is unwilling to continue follow-up through scheduled study visits, the child will be referred back to their primary care provider for continued antibiotic treatment and follow-up.

5.3.5 Termination of Study

The study will be completed when all enrolled subjects have completed follow-up, or when NIDCD following recommendations of the DSMB determines that the study needs to be terminated.

6 STUDY INTERVENTION

The study intervention consists of TTP. Children deemed to be eligible for the randomized phase of the study will be scheduled for evaluation by ENT specialists at each of the participating institutions, and for insertion of TT within 2 weeks in those assigned to receive TTP. TTs will be inserted under general anesthesia, using a small radial incision in the anteroinferior portion of the TM; a Teflon® Armstrong-type tympanostomy tube will be used. All children undergoing TTP will be treated with ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the external auditory canal twice daily for 3 days.

7 STUDY SCHEDULE

See Appendix A for the Schedule of Events table.

7.1 Screening Phase

There are two phases of study participation: screening and randomization. In the screening phase, we will obtain informed consent from the parent(s) of children who have risk factor(s) for rAOM, and follow them prospectively. Risk factors would include for example: (1) age 6-35 months; (2) early age of onset of AOM (<6 months of age), (2) a history of rAOM, (3) a current or recent episode of AOM, (4) episode(s) of AOM during warm-weather months (May–Oct), and (5) exposure to ≥ 3 children for ≥ 10 hours/week.

Potential candidates will be referred for evaluation by clinicians at (1) the CHP Primary Care Center; (2) CNMC Goldberg Children's Health Center; (3) Pediatric PittNet and other practices from Children's Community Pediatrics; (4) other practices in the Pittsburgh area (5) CP&A in the Washington, D.C. area (6) Bardstown, KY.. Medical records will be reviewed for potentially eligible children who have appointments to be evaluated. We will identify those children who are at risk for rAOM and those with a chief complaint of AOM-related symptoms. Parent(s) or legal guardian(s) will be asked by their primary care provider if they are willing to be approached by the research staff in order to discuss the study.

Following a brief introduction of the study by a study clinician or research nurse, the informed consent process will take place with a full explanation of the study and a generous time period to allow the parent to read the consent document and to enter into an exchange of questions and answers. Fully informed, written consent will be obtained from the parent(s) or legal guardian(s) after all questions and discussions have been completed and prior to conducting any study procedures on their child.

Children will be followed in the screening phase until they meet criteria for rAOM, or for 12 months if they do not develop episodes of AOM. During this phase, in order to document whether they experience at least one episode of AOM that would make them eligible for the randomized phase of the study, we will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM. Up to 2 episodes of AOM will be accepted from the medical record review as protocol-defined AOM history. Documentation for such episodes must include one acute symptom and description of a bulging TM. Since the duration of middle-ear effusion is not an outcome measure of this investigation, we will not evaluate children following the end of therapy, unless the parent has concerns that the child has not improved. AOM during the screening phase will be defined as: (1) acute symptoms (at least one) accompanied by the presence of middle-ear effusion and moderate or marked TM bulging, or slight TM bulging accompanied by either otalgia or marked TM erythema, or (2) purulent otorrhea not due to otitis externa. Acute symptom(s) will be defined by a score ≥ 2 on the AOM-SOS scale (version 4.0) for episodes evaluated by study personnel, or documentation in the

medical record by other providers for all other episodes. Observation of at least one AOM episode by study personnel will be required for subjects to move to the second, *randomization phase* of the study. Children who have not developed AOM for a 12-month period during the screening phase will be discharged from the study.

If a participant is found to have bilateral otitis media with effusion for 6 months, we will inform the primary care provider who will determine subsequent management. In addition, if the parent has any concerns about the child's hearing or development, we will refer the child to the primary care provider or ENT specialist, as appropriate.

7.1.1 Screening Phase - Enrollment - Visit

After receiving parental/legal guardian written consent, the following activities will be performed:

- Screening criteria will be reviewed.
- An AOM-SOS scale will be completed by parents, when AOM is present on enrollment, before any discussion of current symptoms.
- We will explain to the parent(s)/legal guardian that over the next 12 months we would like to follow the subject when any upper respiratory symptoms develop and persist for ≥ 5 days or when there is any suspicion that AOM has recurred, in order to evaluate for the recurrence of AOM. We will indicate that we will assess and manage episodes of AOM according to the standard of care and prescribe treatment as necessary.
- We will initiate email reminders to be sent bi-weekly to encourage parent(s)/legal guardian to call study personnel with any concerns for persistent upper respiratory symptoms or symptoms suggestive of AOM. The email will include a question requiring a yes/no response concerning the presence of upper respiratory symptoms. If the parent indicate that their child has a cold, study staff will call the family to evaluate the need for a subsequent screening visit.
- Baseline data will be collected about AOM risk factors (e.g., exposure to other children, early AOM history, AOM during warm weather months [May-Oct], and history of AOM in the past 6 months), and about socioeconomic factors (educational level of parents and type of health insurance), and demographics.
- The child's overall medical history will be obtained.
- A targeted physical examination, including pneumatic otoscopy, will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- When possible with an episode of AOM, a nurse or clinician will capture a TM image (A TM image will not be able to be captured at the ED of CHP of UPMC).

7.1.2 Screening Phase Sick Visit

Children will be seen for a subsequent visit during the screening phase because of new, continuing or worsening symptoms of an upper respiratory infection (either clinical decision or parent request). Antibiotics will be prescribed at the investigators decision generally following a stepwise approach (see below) for episodes of AOM. Our study team will ask parents to bring their children to be examined by our study team if they develop persistent respiratory symptoms or within 48 hours after the development of any symptom suggestive of AOM.

- AOM-SOS scale will be completed by parents before any discussion regarding current symptoms.
- Temperature will be measured and weight obtained if clinically indicated.
- We will obtain a history concerning any medical care visits at which AOM was diagnosed since the last study visit.
- A targeted physical examination, including pneumatic otoscopy, will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- When possible with an episode of AOM, a nurse or clinician will capture a TM image (A TM image will not be able to be captured at the ED of CHP of UPMC).
- Episodes of AOM occurring during the screening phase of the study will receive stepwise therapy with amoxicillin (90 mg/kg in two divided doses for 10 days), amoxicillin-clavulanate (90/6.4 mg/kg in two divided doses for 10 days), and if response is considered inadequate, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the AAP guidelines.⁵

7.2 Randomization phase and treatment assignment

Children aged 6-35 months who meet inclusion criteria for rAOM will be eligible to participate in the Part 2, *randomization phase* of the study. This enrollment visit may occur on the same day as a *screening* sick visit at which the participant became eligible for randomization.

We will define rAOM as the occurrence of ≥ 3 AOM episodes in 6 months or ≥ 4 episodes in 12 months with at least 1 episode in the preceding 6 months. One of these episodes must be documented by trained study personnel prior to enrollment in the randomized phase of the study.

- Eligibility criteria will be reviewed.
- Once the study has been explained, all questions have been answered, and informed consent has been obtained, eligible children will undergo central randomization within strata based on age (6-11 months, 12-23 months and 24-35 months) and history of

exposure to other children (non-exposed vs. exposed to ≥ 3 children ≥ 10 hours/week). Children will be assigned in a 1:1 ratio either to undergo TTP or to be managed nonsurgically.

- If a child is assigned to undergo TTP, a visit with the otolaryngologist and the surgery will be scheduled to take place within 2 weeks of randomization.
- Randomization information will be programmed into the eCRF.
- The AOM-SOS scale will be completed by parents before any discussion regarding current symptoms.
- Vital signs (temperature, heart and respiratory rate) and weight will be measured, if clinically indicated.
- Medical history will be reviewed.
- A targeted physical examination, including pneumatic otoscopy, will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- A nurse, or a clinician licensed to make medical diagnoses, will capture a TM image, when possible.
- An NP specimen will be collected at randomization in children aged 6 to 23 months every 16 weeks or about three times a year.
- A throat culture will be collected at randomization in children aged ≥ 24 months every 16 weeks or about three times a year.
- Quality of life assessment will be completed at randomization and at every other visit.
- The study team will call the family after the surgery to schedule a follow-up study visit.

Randomization Phase Follow-up every 8 weeks (7-9 weeks window)

Children enrolled in the study will be evaluated every 8 (± 1) weeks and at any time parent(s) or legal guardian(s) suspect the occurrence of AOM. If a subject is diagnosed with AOM at a non-participating clinical site, parents will be asked to bring the subject to a study site within 48 hours for further evaluation. The AOM-SOS scale will be completed by parents before any discussion regarding the current symptoms.

- Temperature and weight will be measured if clinically indicated.

- A targeted physical examination, including pneumatic otoscopy, will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- A nurse, or a clinician licensed to make medical diagnoses will capture a TM image for each episode of AOM when possible. Normal images will be obtained periodically.
- An NP specimen or throat culture will be collected at every other follow-up visit or about three times a year.
- Update history of AOM episodes.
- Regarding children diagnosed with AOM--both those with intact TMs and those with tube otorrhea--their parents will complete an electronic memory aid daily through Day 11 to determine whether symptoms on the AOM-SOS have resolved (score of 0 on all 5 items), Parents will be asked to provide an end date for symptoms. Medication-related adverse events (PDD, diaper rash) will be collected.
- Parents will be asked to complete an electronic memory aid through day 11. Parents will be asked to provide an end date for symptoms. We will also track the occurrence of medication-related adverse events (PDD, diaper rash). For parents completing the paper memory aid, they will receive a phone call at day 5 to determine if symptoms have resolved. If symptoms have not resolved at day 5, parents completing the paper memory aid will also be called at day 12.
- Otorrhea occurring in children with TT in place will be considered indicative of acute infection. A specimen of the discharge for standard microbiologic assessment will be obtained, when possible from the tube orifice directly.
- Otorrhea will be treated with topical ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the affected ear twice daily for 10 days.
- Otorrhea persisting after 7 days of treatment will be considered an inadequate response, and we will initiate empiric therapy with amoxicillin-clavulanate (90/6.4 mg/kg/day in two divided doses), followed by culture-directed therapy 48 hours later.
- Children randomized to nonsurgical management will receive stepwise therapy with amoxicillin-clavulanate as above for 10 days, and in the event of inadequate response, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the AAP guidelines.⁵
- Study personnel will review adverse events, utilization of health care and related resources, and receipt of concomitant medications since the preceding visit.

- Quality of life assessment and Caregiver Impact questionnaire will be collected at every other visit (i.e, about every 16 weeks).
- An episode of AOM will be considered a recurrence if it has occurred at least 17 days after the start of treatment for a preceding AOM episode.
- If a TT becomes obstructed, we will follow a standardized protocol that includes ofloxacin (5 drops twice daily for 14 days), followed by careful suction in clinic.
- If a TT becomes extruded within 6 months of insertion, it will be reinserted by ENT specialists only if the child develops at least 2 episodes of AOM within 3 months. Beyond 6 months, a TT will be reinserted by ENT specialist only if the child meets criteria for rAOM (3 AOM episodes in 6 months, 4 AOM episodes in 12 months).
- Follow-up visits are scheduled every 8 weeks until the end of study participation, which is 2 years following randomization.
- To determine the impact of study-related monitoring on health care utilization, at each routine study-related visit, parents/legal guardians will be asked whether the study visit either had no influence on scheduling, or prevented, or induced a primary-care provider visit.

7.2.2 Randomization Phase Sick Visit

- Children will be seen for a sick visit because of new, continuing or worsening symptoms of an upper respiratory infection. (either clinical decision or parent request). Antibiotics will be prescribed as necessary for episodes of AOM according to protocol.
- The AOM-SOS scale will be completed by parents before any discussion regarding current symptoms.
- Temperature will be measured and weight obtained if clinically indicated.
- A targeted physical examination, including pneumatic otoscopy, will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- When there is a diagnosis of AOM, a nurse, or a clinician licensed to make medical diagnoses, will capture a TM image when possible. A TM image will usually not be obtained if AOM is not diagnosed.
- Otorrhea occurring in children with TT in place will be considered indicative of acute infection. A specimen of the discharge for standard microbiologic assessment will be obtained, when possible from the tube orifice directly.

- Otorrhea will be treated with topical ofloxacin (Floxin® 0.3%, 5 mL) 5 drops into the affected ear twice daily for 10 days.
- Otorrhea persisting after 7 days of treatment will be considered an inadequate response, and we will initiate empiric treatment with amoxicillin-clavulanate (90/6.4 mg/kg/day in two divided doses) followed by culture-directed therapy 48 hours later.
- Children randomized to nonsurgical management will receive stepwise therapy with amoxicillin-clavulanate as above for 10 days, and in the event of inadequate response, ceftriaxone (75 mg/kg intramuscularly, repeated in 48 hours), as recommended in the AAP guidelines.⁵
- Parents of children diagnosed with AOM, both those with intact TMs and those with tube otorrhea, will complete an electronic memory aid (or a paper memory aid in the event the electronic memory aid is unavailable) daily through Day 11 to determine whether symptoms on the AOM-SOS have resolved (score of 0 on all 5 items on Day 5). Parents will be asked to provide an end date for symptoms. Medication-related adverse events (PDD, diaper rash, otorrhea) will be collected up until day 11 in the electronic aid. In the event parents do not have access to e-mail or the electronic diary is not available, they will be given a paper diary. When completing a paper diary, the study team will call on day 5 to check on the child.
- Parents will receive a phone call on day 12 (+/-2 days) in order to track symptoms that may not have resolved on the Day 5 paper memory aid. Parents will be asked to provide an end date for symptoms. We will also track the occurrence of medication-related adverse events (PDD, diaper rash, otorrhea). Parents of children, whose health is back to normal at the day 5 diary entry, will not receive a phone call.
- If an episode of AOM has occurred, an NP specimen or throat culture will be collected.
- Study personnel will review and record selected AEs/SAEs, AOM symptom status, fever, diarrhea, and concomitant medications on the appropriate eCRFs.
- To determine the impact of study-related monitoring on health care utilization, at each study sick visit, parents/legal guardians will be asked whether the study visit either had no influence on scheduling, or prevented, or induced a primary-care provider visit.
- We will schedule an 8-week follow-up visit.

7.3 End-of-Study Visit (± 4 weeks)

- Children will undergo an end-of-study visit 2 years after randomization.

- The AOM-SOS scale will be completed by parents before any discussion regarding symptoms.
- An NP specimen or throat culture will be collected if appropriate based on the every other visit schedule.
- A quality of life assessment and caregiver impact questionnaire will be completed.
- Parents will be asked to rate their level of satisfaction with the child's assigned medication using a 5-point scale.
- A targeted physical examination, including pneumatic otoscopy, will be performed by a study-licensed clinician listed on the FDA Form 1572 as the site principal investigator or sub-investigator.
- Temperature will be measured, if appropriate.
- If the child is found to have AOM, treat with the provider's choice of antibiotic.
- Any recommended follow-up should occur with the child's primary care provider.
- Any adverse event that has occurred since the last visit will be recorded.
- Any protocol-specific concomitantly administered medications will be recorded on the concomitant medication form.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Medical History: Will be obtained by review of medical records and interview of the parents/legal guardians. The medical history is completed at the time that the subject is consented for the screening period and will be reconfirmed at the time of randomization to capture pertinent or significant medical history events including drug allergy, chronic disease, or surgery.

Concomitant Medications: Will be obtained by review of medical records and interview of the parents/legal guardian. During the *Screening Phase*, we will inquire about the number of antibiotic courses the child has received during the preceding 6 months. During the *Randomization Phase*, medications taken by the subject at randomization and through the end-of-study visit which are specific to the treatment of AOM, management of AOM symptoms and adverse events related to AOM treatment will be recorded (e.g., antibiotics, ear drops, ibuprofen, acetaminophen, topical antifungal medications).

Physical Examination: At enrollment/randomization, vital signs (temperature, heart and respiratory rate) and weight (unless there is a weight measurement recorded in the previous month) will be measured and a targeted physical examination (including pneumatic otoscopy and, when possible, a capture of the TM image) will be performed by appropriate study personnel. At all visits following enrollment in the screening or randomization phases, pneumatic otoscopy will be performed, and if AOM is diagnosed, an image of the TM will be captured when feasible.

Memory Aids: Parents/legal guardians will be provided with an electronic memory aid to assess AOM symptom status using the AOM-SOS scale. The AOM-SOS scale (version 4.0) measures five discrete items: tugging of ears, crying, irritability, difficulty sleeping and fever. Parents will be asked to rate these symptoms on enrollment in the randomized trial (Day 1), daily (Days 1-11) in comparison with the child's usual state, as "none," "a little," or "a lot," with corresponding scores of 0, 1, and 2. Thus, total scores range from 0 to 10, with higher scores indicating greater severity of symptoms. Frequency of bowel movements and the consistency of stools will also be recorded in the electronic memory aid to determine the occurrence of PDD.

Determination of direct medical costs: Costs will be ascertained by collecting data from two complementary sources: parent reports and medical records. First, at each study visit (every 8 weeks), we will ask parents about the number and type of encounters with healthcare providers (emergency department, hospitalizations, surgeries, ENT, primary care provider) and about antibiotic use. Cost of research-only visits will not be included in the calculation of the costs, except in cases where parents state that the visits prevented a visit for an otitis media-related concern. Second, we will review each subject's medical records to ensure that all visits to health care professionals have been captured.

Parent questionnaires: A validated OM-6 quality of life (OM-6 QOL) survey tool will be administered to the parent at every other visit (every 16 weeks) after the randomization visit. A CIQ will be administered to the parent at every other visit (every 16 weeks) after the randomization visit to determine the impact of study related monitoring on health care utilization. At each routine study-related visit, parents/legal guardians will be asked whether the study visit either had no influence on scheduling, or prevented, or induced a primary care provider visit.

Parental satisfaction with treatment: Will be evaluated using a 5-point scale (very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied and very satisfied).

Utilization of Health Care and Related Resources: Parents will be asked about their utilization of health care (ED, urgent care center, primary care provider) and related services for subjects enrolled in the study. The survey data will be obtained at the time of follow-up assessment visits. As noted above parents/legal guardians will be asked whether the study visit either had no influence on scheduling, or prevented, or induced a primary care provider visit. Parents will be also asked about the number of sick days, the number of days in which the parent(s)/legal guardian(s) could not work due to the child's being sick; and the number of days on which alternative day-care arrangements were necessary for sick children.

8.2 Concomitant Medications/Treatments

At each visit, medications taken by the child at randomization and through the end-of-study visit that are specific to the management of AOM or to side-effects of treatment, i.e., antibiotics, ear drops, ibuprofen, acetaminophen, and topical antifungal medications will be recorded.

Special Procedures

The study clinician at each participating study site will conduct an otoscopic examination and, when possible, capture an image of the TM. Participating clinical study site facilities will be equipped with otoendoscopes to allow capture of digital photographs into the eCRF. Although pneumatic otoscopic diagnosis will be considered determinative, TM images will be used to support classification of primary outcome (i.e., presence or absence of a need for further antimicrobial therapy). Similarly, by enabling study clinicians at participating study sites to discuss otoscopic findings with the investigators via computer or cellular phone, these images are expected to enhance the accuracy of both entry diagnosis and classification of treatment outcome.

8.4 Clinical Laboratory Evaluations

During the screening period, children will only be evaluated for episodes of AOM; bacterial cultures will not be obtained. Once participants have met criteria for recurrent AOM, they enter

into the randomization phase of the study. At the enrollment visit in this phase, we will obtain written informed consent for this portion of the study. We will then obtain an NP specimen in subjects ages 6 to 23 months from one of the nares, using a sterile, flexible, thin, nylon-flocked swab. A throat culture will be collected from subjects aged ≥ 24 months. These will be obtained at the time of the randomization visit, and subsequently at every other study follow-up visit (~ q 16 weeks). Personnel will wash their hands before and after the procedure and use proper personal protection equipment as necessary when collecting NP swabs, specifically gloves and face and eye protection. Depending on children's age, they either will be lying on the exam table with hands and head held securely by an assistant, or sitting in the parent's lap. We will lift the subject's chin to tip the nose slightly upward; introduce the swab gently along the floor of the nasal cavity, close to the nasal septum, until the pharyngeal wall is reached, usually about 4- 5 centimeters, taking care not to insert the swab upwards. The nasal "tunnel" goes straight back toward the occiput and not toward the eyes. The swab will never be forced. If an obstruction is encountered, we will try using the other nostril; if that is unsuccessful we will not proceed further. The swab will be held in place for up to 5 seconds. If at any time during follow-up the parent refuses to have an NP specimen obtained, we will attempt to collect a nasal swab from the middle turbinate in its place.

We will place the swab into the transport tube so that the tip is immersed in the media, and attach preprinted labels to the transport tube including study name, visit date, subject initials and subject ID number. The swab can be kept at room temperature for up to 20 minutes, and then must be refrigerated in a specimen refrigerator until transport to the CHP Microbiology Laboratory (Micro Lab). When same day transport is not possible, the swab may be held overnight in the local site's refrigerator, but it must be transported the following day. Per the current standard procedures and guidelines, it is necessary to monitor the temperature of equipment where specimens are stored, and record temperatures on days that specimens are stored in the refrigerator (no need to record on weekends or holidays). Refrigerator temperatures will be held at 2-8°C while specimens are stored inside.

When information is entered into the electronic database that the specimen has been collected, the Micro Lab will be so notified and the specimen will be transported. The Micro Lab will enter into the database the date that the swab is either plated or frozen. In the event of no growth from the sample, any delay of >72 hours in sample arrival to the Micro Lab will be noted by the Lab on the worksheet and in the electronic database. The Micro Lab will notify the PI promptly of any potential issues with specimen transport such as an open or spilled specimen or missing information on the label. All specimens will be processed upon arrival at the Micro Lab. In some cases, however, a specimen may be frozen temporarily until microbiological analysis can be performed. After NP swabs are processed, they will be frozen and stored in glycerol stock in an 80°C freezer for potential further studies.

NP swabs will be inoculated onto three plates: chocolate agar, 5% sheep's blood agar with a P disk placed onto the TSA plate, and a chocolate agar plate, and will incubate overnight with 5% CO₂ at 37°C. Organisms that grow on chocolate agar but not on the blood agar plates will be considered as potentially being *H. influenzae*. We will look for growth in areas proximal to isolates of *S. aureus* on blood agar plates where the presence of beta-hemolysis may allow

growth of *H. influenzae* on the TSA plate. Based on the presence of hemolysis and the pattern of growth an assessment for potential growth of *H. influenzae* can be made. These colonies will then undergo investigation of their Gram-staining properties and colonial morphology. If they are Gram-negative coccobacillary rods, we will subculture colonies onto a *Haemophilus* Quad plate (Remel) to verify if they require X and V factors. Based on the presence of hemolysis and the pattern of growth an assessment for growth of *H. influenzae* can be presumed. For *H. influenzae*-like isolate characterization we will distinguish *H. influenzae* from *H. haemolyticus*. These closely related, but genetically distinct, strains will be distinguished by testing for presence of *igtC* and *iga* by PCR.⁵⁷ Strains positive for both genes will be designated *H. influenzae* and strains negative for both, *H. haemolyticus*. Rare strains that are discordant for these two genes will be considered variants. After confirmation, *H. influenzae* strains will be tested by PCR for presence of capsule genes *bexA* and *bexB*, and strains positive for these genes will be tested for specific capsule type;^{58,59} *bexA* and *bexB* negative strains will be considered non-typeable. For isolates confirmed to be *H. influenzae*, we will perform a cefinase test on HTM agar to evaluate for the presence of β -lactamase production. Isolates of *H. influenzae* that are β -lactamase negative will undergo antimicrobial susceptibility testing against ampicillin using the Remel *in vitro* fast MIC test according to the manufacturer's recommendations.

For *S. pneumoniae* we will inspect the 5% sheep's blood TSA plate looking for the presence of alpha-hemolytic colonies. Suspicious colonies will undergo Gram-staining to confirm the presence of Gram-positive cocci in pairs and chains. Suspicious colonies will be sub-cultured on a TSA blood agar plate with a P-disk placed on the media, and colonies that show inhibition to the P-disk will be confirmed as *S. pneumoniae*. Colonies that do not have a strong morphologic appearance of *S. pneumoniae* will be considered as non-pneumococcal strains. Isolates considered to be *S. pneumoniae* will undergo sub-culture on a TSA blood agar plate with an oxacillin disk for Kirby Bauer susceptibility testing. Isolates of *S. pneumoniae* with zones of inhibition of ≤ 19 mm to oxacillin are considered to be potentially resistant to penicillin and undergo broth microdilutional Micro Scan (Siemens) testing to determine specific minimum inhibitory concentrations (MICs) and susceptibilities to other agents using the appropriate recommended panel for *S. pneumoniae* isolates (penicillin, amoxicillin/clavulanate, ceftriaxone, erythromycin, clindamycin, levofloxacin and trimethoprim/sulfamethoxazole). Isolates whose zones of inhibition are > 19 mm are considered to be penicillin-susceptible and will not undergo further susceptibility testing. Serotyping of confirmed isolates of *S. pneumoniae* is carried out using Statens Serum Institute kit with a Quellung reaction of serotype-specific antisera according to the manufacturer's recommendation.

For *Moraxella catarrhalis* we will inspect the 5% sheep's blood TSA plate and chocolate plate looking for the presence of gray to white, opaque smooth, dry colonies. These colonies will be sub-cultured and evaluated. Colonial morphology demonstrating the appropriate appearance will also help identify *M. catarrhalis*. Suspicious colonies undergo Gram-stain to confirm the presence of Gram-negative diplococci. Suspicious colonies will be sub-cultured and an *M. catarrhalis* disk (containing butyrate esterase) will be used to confirm the identification. Butyrate hydrolysis is a key test in differentiating *M. catarrhalis* from *Neisseria* spp. Further susceptibility

testing will not be performed for these isolates as they are all assumed to be β -lactamase positive.

8.4.1 Specimen Preparation, Handling, and Shipping

All clinical microbiological samples (NP swab specimens) obtained from all study participants enrolled at all participating clinical study sites will be processed at CHP according to guidelines established by the Micro Lab. This laboratory will identify all organisms cultured from the samples. Instructions for specimen preparation, handling, and storage are included in the protocol-specific MOP.

The NP swab specimens will be sent to
Microbiology Laboratory
Children's Hospital of Pittsburgh of UPMC
4401 Penn Ave.
Pittsburgh, PA 15224

Instructions for specimen shipment are included in the protocol-specific MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse Events

Adverse Event (AE): ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

In the Screening Phase, only events meeting the criteria for SAEs are collected. In the Randomization Phase, select adverse events are collected from Day 1 (enrollment) through the end of study visit (2 years after randomization). These consist mainly of PDD, diaper rash necessitating the prescription of topical antifungal therapy and otorrhea. Other AEs of a severe nature defined below are recorded. We will record details concerning AEs on the appropriate eCRF, including event description, date of onset, assessment of severity and relationship to study intervention, and date of resolution/stabilization. Investigators or sub-investigators with the training and authority to make a diagnosis and listed on the FDA Form 1572, i.e., MD, PA, Nurse Practitioner, DO, or DDS will assess the relationship of the AE to study intervention. AEs are documented appropriately regardless of relationship and followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE.

Elective procedures requiring hospitalization will not be considered SAEs.

AEs characterized as intermittent will require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

Severity of Event: All AEs will be assessed by the study clinician. At the time of an AOM episode, the AOM-SOS scale, a protocol-defined grading system, will measure the parent's estimate of the presence and severity of five discrete items: tugging of ears, crying, irritability, difficulty sleeping and fever.

For events not included in the AOM-SOS scale, the following guidelines are used to quantify severity:

- **Severe:** events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Life-threatening:** any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE are documented to allow an assessment of the duration of the event at each level of intensity. AEs characterized as intermittent will require documentation of onset and duration of each episode.

Relationship to Clinical Antibiotic Treatment or Study Intervention (TTP): The study clinician's assessment of an AE's relationship to the clinical antibiotic treatment or study intervention (TTP) will be part of the documentation process, but will not be a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs will have their relationship to clinical antibiotic treatment and study intervention (TTP) assessed using the terms: related or not related. Factors to consider in determining a causal relationship include: (1) whether the event is described in the investigator's brochure or product insert; (2) whether a temporal relationship exists between the event and the administration of clinical antibiotic treatment or study intervention (TTP); (3) whether a possible alternative etiology has been identified; and (4) whether it is biologically plausible that the event may be related to the product. To help this assessment, the following guidelines will be used:

- **Related** – There is a reasonable possibility that clinical antibiotic treatment or study intervention caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between clinical antibiotic treatment or study intervention (TTP) and the adverse event.
- **Not Related** – There is not a reasonable possibility that the administration of clinical antibiotic treatment or study intervention caused the event.

9.2.2 Reactogenicity

Not applicable.

9.2.3 Serious Adverse Events

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction will be considered "serious" if, in the view of either the study clinician or sponsor, it results in any of the following outcomes:

- death
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization, or
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may nonetheless be considered serious when, based upon appropriate medical judgment they may jeopardize the child's well-being and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

All SAEs will be:

- Assessed by a study physician licensed to make medical diagnoses and listed on the FDA Form 1572 as the principal investigator or sub-investigator at each site.
- Recorded on the appropriate SAE CRF.
- Followed through resolution by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the principal investigator or sub-investigator at each site.
- Reviewed and evaluated by an ISM, the DSMB (periodic review unless related), NIDCD, and the IRB.

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

AE/SAEs will be documented, reported and followed appropriately.

In order to evaluate the effect of TTP on the colonization of the nasopharynx, NP specimens will be obtained for culture with identification of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. In the absence of illness, detection of these organisms in the nasopharynx will be considered a normal finding, whether or not any of these organisms exhibit antimicrobial resistance.

9.3 Reporting Procedures

All AE and SAE occurrences will be recorded for all subjects from Day 1 (enrollment) through the final study visit 2 years after randomization.

Safety reporting will occur whenever AEs, SAEs, or PDD occur among study participants. All participating sites will report SAEs on the SAE Report Form to the principal investigator and the ISM immediately.

SAEs related to clinical antibiotic treatment or study intervention (TTP) will be reported to the IRB within 24 hours of awareness at the site. Unexpected adverse reactions of moderate severity and related to clinical antibiotic treatment or study intervention (TTP) will be reported to the IRBs within 5 days. Monthly line-item reports of all SAEs and a 6-month report of all AEs will be submitted to the DSMB and NIDCD. The principal investigator and study team will not contact the DSMB or communicate with the DSMB directly. All communication and materials will be sent through the DSMB support contractor and NIDCD, and the study team will not review closed-session reports.

9.3.1 Serious Adverse Events

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on a SAE form to the CHP Data Coordinating Center, at the following address:

Kristin YahnerData Coordinating Center
Children's Hospital of Pittsburgh of UPMC
CHOB 3rd Floor
3414 Fifth Avenue
Pittsburgh, PA 15213

SAE Hot Line: Dr. Hoberman 1-999-3277

SAE FAX Phone Number:412-692-5507

SAE Email: Kristin.yahner@chp.edu In addition to the SAE form, selected SAE data fields must will also be entered into the central database. (Please see the protocol-specific MOP for details regarding this procedure.)

Other supporting documentation of the event may be requested by the NIH/NIDCD and will be provided as soon as possible.

The study coordinator or principal investigator should report by telephone, fax, or email all deaths and life-threatening SAEs (including laryngospasm, anaphylaxis, and cardiopulmonary

resuscitation) within 24 hours of learning of the event to the NIDCD program officer and to the IRB as specified in the protocol. This immediate report should be followed within 7 days by a detailed written report from the study coordinator or principal investigator to the NIDCD, IRB as required by the local IRB, and all participating investigators. All other SAEs should be reported to the NIDCD within 7 days, followed by a detailed written report to, NIDCD, IRB, and all participating investigators within 15 days.

9.3.2 Reporting of Pregnancy

Not applicable.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution is defined as the return to pretreatment status or stabilization of the condition (the investigator does not expect any further improvement or worsening of the event).

9.5 Halting Rules

Further enrollment and study intervention administration will be halted for DSMB review and recommendation if:

- Any death occurs that was not the result of trauma or accident.

The IRB and NIDCD retain the authority to suspend enrollment for the entire study at any time.

9.6 Safety Oversight (ISM plus DSMB)

Safety oversight will be conducted by a DSMB which is an independent group of experts that review study data, monitor subject safety and advises NIDCD and the PI. DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to the study. The DSMB will consist of five voting members including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise. Independent Safety Monitors (ISMs) are physicians with relevant otitis media and/or pediatric infectious diseases expertise whose primary responsibility is to provide timely independent safety monitoring. The ISMs (one each for Pittsburgh, PA, Washington, DC and Bardstown, KY) will not be directly involved in the trial, will not be under the investigators' supervision, and will have no financial, intellectual, proprietary, or professional interest in the outcome of the trial. An ISM is assigned to each participating clinical study site, is in close proximity to the site and has the authority to readily access study participant records. The ISM reviews any SAE that occurs at the participating clinical study site in real time and

provides an assessment to the study Co-PIs (A. Hoberman and D. Preciado) and the DSMB per the DSMB charter.

To avoid any appearance of conflict of interest, it is critical that DSMB members not be involved in the study, have no vested interest in its outcome, have no ties to the study investigators and have no financial ties to any commercial concerns likely to be affected by the study's outcome.

The DSMB will review study and safety data at the following time points:

- At specified times during the course of study as defined in the DSMB Charter.
- An interim analysis for clinical efficacy will be conducted after 120 subjects have been enrolled and completed follow-up.
- Ad hoc when a halting rule is met, or as otherwise needed.

The DSMB will meet regularly (usually teleconference, alternatively e-mail) to monitor the cumulative safety data during the participant follow-up period. Typically, the DSMB will meet every 6 months; and in no instance will more than 12 months elapse between DSMB review of cumulative safety data after the first subject has been enrolled. The DSMB will monitor the study according to the guidelines specified in the study protocol and the operating procedures established at the initial meeting, unless the DSMB determines during the course of the trial that modification of the guidelines is in the best interest of the study and its participants. Such a decision may be based on new information that emerges during the course of the study (e.g., publication of the results of a similar trial), recognition that initial study assumptions were inappropriate, or the occurrence of an unanticipated scenario.

The DSMB will operate under the rules of an approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews and meetings will also be defined in the charter. Procedural issues include: the board's meeting frequency; the types and formats of reports it will receive from the Data Coordinating Center (DCC), the policy on whether and how the members may be unblinded; which interim data, if any, may be released to the study investigators (e.g., overall AE rate); and how minutes will be taken and distributed.

Before initiation of the trial, the DSMB will review the study protocol (particularly the specific outcome definitions), halting rules, the interim and final analysis plan, the procedures for recording and reporting SAEs, and the data and safety monitoring plan (including draft shells of safety reports and tables). The informed consent document/process also will be inspected to ensure that all required elements have been included in language understandable to parents/legal guardians of children to be enrolled in the trial.

Study data will be reviewed by the DSMB according to the charter for this study. Trial review issues include: study progress, including an assessment of data quality (monitored monthly); efficacy outcomes and AE/SAE data, including out-of-range laboratory results (ongoing

monitoring); any pertinent new information (monitored every 6 months); study procedures designed to protect the privacy of the subjects and the confidentiality of the data (monitored weekly); interim analysis, and final conclusions evaluating benefit-to-risk ratio of study participation. The DSMB will review applicable data that will include but not be limited to enrollment, demographic, and efficacy outcomes; laboratory and safety data which may include AE/SAEs, concomitant medications, memory aid data, and laboratory results (NP swab specimen cultures); TM images, otoscopic findings, and any other physical findings. Interim statistical reports may be generated as deemed necessary and appropriate by the PI. Comparative results will be presented to the DSMB in closed reports and closed sessions will be attended only by voting members of the DSMB and possibly a member of NIDCD staff. As an outcome of each review and meeting, the DSMB will make a recommendation at that time as to the advisability of proceeding, modifying, or terminating the study.

SAE Reporting: The study coordinator or principal investigator should report by telephone, fax, or email all deaths and life-threatening SAEs (including laryngospasm, anaphylaxis, and cardiopulmonary resuscitation) within 24 hours of learning of the event to the NIDCD program officer and to the IRB as specified in the protocol. This immediate report should be followed within 7 days by a detailed written report from the study coordinator or principal investigator to the NIDCD, IRB as required by the local IRB, and all participating investigators. All other SAEs should be reported to the NIDCD within 7 days, followed by a detailed written report to, NIDCD, IRB, and all participating investigators within 15 days.

NIDCD or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of the study. The NIDCD Scientific Officer is empowered to stop study enrollment if adverse events that meet the halting criteria are reported. The NIDCD Scientific Officer and the ISM will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during the study.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protections, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet NIDCD, University of Pittsburgh, ICH E6 (GCP) and applicable regulatory guidelines, and that the study is conducted in accordance with the protocol and applicable standard operating procedures.

Independent clinical study site monitoring will be conducted as detailed in the clinical monitoring plan. This will include on-site monitoring visits at standard intervals, or more frequently as necessary, throughout the study to oversee data collection, review source documentation case report forms and informed consents, ensure GCP and regulatory compliance and resolve data queries. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol compliance. CRAs will have reasonable access to the participating clinical study site, study personnel, and all study documentation. CRAs will meet with participating clinical study site investigators to discuss any problems and actions to be taken and document visit findings and discussions. Clinical monitoring reports will be submitted to the study principal investigator.

11 STATISTICAL CONSIDERATIONS

11.1 Introduction

The study is a phase 3, multicenter, randomized, clinical trial in children aged 6-35 months with rAOM. Its goal is to determine whether TTP (experimental group) compared with nonsurgical management (antibiotics-treated; control group) will meaningfully improve the children's AOM experience over the succeeding 2 years. This document gives details on the planned statistical analyses for efficacy and safety for the study.

11.2 Objectives

The primary objective of the study is to determine the efficacy of TTP for rAOM, compared with the efficacy of episodic nonsurgical management (i.e. conventional antibiotic therapy), in children aged 6 to 35 months who have reached conventional indications for TTP, i.e. at least 3 episodes in 6 months or 4 episodes in 1 year with the most recent episode having occurred within the immediately preceding 6 months. Secondary objectives are (1) to examine whether TTP will be followed by reduced nasopharyngeal (NP) carriage rates of penicillin-nonsusceptible *S. pneumoniae* and/or β -lactamase-producing *H. influenzae* over the 2-year period following randomization and (2) to compare cost-effectiveness of TTP in these children relative to that of nonsurgical management.

Study Design

The goal of the study is to determine whether TTP compared with nonsurgical management will meaningfully improve the children's AOM experience over the succeeding 2 years. A total of 240 children diagnosed with rAOM will be enrolled at participating clinical study sites, namely, CHP of UPMC, Pittsburgh, PA and its affiliated Pediatric PittNet Practice-Based Research Network, and CNMC, Washington, DC and its affiliated CP&A as well as Bardstown, KY, Rochester, NY and Morgantown, WV. Participating clinical study sites are projected to enroll approximately 100 eligible children per year over a period of 2.5 years.

Once the study has been explained, all questions have been answered, and written informed consent has been obtained, eligible subjects will undergo central randomization within strata based on age (6-11 months, 12-23 months and 24-35 months) and degree/history of exposure to other children (non-exposed vs exposed to ≥ 3 children ≥ 10 hours/week). Children will be assigned in a 1:1 ratio to either undergo TTP or to be managed nonsurgically. Randomization information will be programmed into the eCRF so that for children assigned to undergo TTP,

study personnel will be able to schedule a visit with the otolaryngologist and TTP within 2 weeks.

11.3 Analysis Populations

11.4.1 Intent-to-Treat Population (ITT)

The ITT population will consist of all children who are randomized and who receive follow-up of any extent. No protocol violations will lead to exclusion from the intent-to-treat population. Children in the intent-to-treat population will be grouped according to the treatment assigned by the randomization procedure. This population will constitute the subjects for the primary and secondary efficacy analyses of study data as well as for safety analyses.

11.4 Study Assessments

11.5.1 Baseline Assessments

The baseline visit will occur at the time of enrollment into the randomized part of the study. Baseline data will include demographics, medical history, medications use history, physical examination findings, and microbiological data (from the NP specimen collected). Randomization of eligible patients will occur after these assessments.

11.5.2 Efficacy Assessments

11.5.2.1 Primary Efficacy Variable

The primary study endpoint is the rate of AOM episodes during the 2-year follow-up period.

11.5.2.2 Secondary Efficacy Variables

1) Treatment Failure

Children will be deemed to have experienced treatment failure if they develop at any time any of the following:

- a. 2 AOM recurrences within 3 months, 3 AOM recurrences within 6 months, or 4 AOM recurrences within 12 months
- b. ≥ 3 severe AOM recurrences within 12 months, with “severe” defined as showing either:
 1. Moderate or severe otalgia or temperature $>39^{\circ}\text{C}$
 2. AOM-SOS score >6 on Day 1
- c. Persistent MEE for ≥ 12 successive months

- d. Otorrhea for ≥ 45 days cumulatively within a 12-month period
 - e. TM perforation for ≥ 90 days following extrusion of TT
 - f. PDD (associated with antimicrobial therapy for AOM) for ≥ 30 days cumulatively within a 12-month period, or treatment with intravenous fluids for PPD (associated with antimicrobial therapy for AOM) on ≥ 2 occasions
 - g. Performance of TTP in children assigned originally to the nonsurgical treatment group
 - h. Hospitalization for any otitis media-related reason, e.g. (1) unplanned admission overnight after surgery that was originally planned as ambulatory; (2) mastoiditis; (3) persistent otorrhea caused by pathogens resistant to oral antimicrobials; and (4) PDD (associated with antimicrobial therapy for AOM) severe enough to require hospitalization.
 - i. Anesthesia reactions, to include laryngospasm, anaphylaxis, or a need for cardiopulmonary resuscitation during surgery;
 - j. Receipt of ≥ 45 days cumulatively of systemic antimicrobials for AOM within a 12-month period
- 2) Frequency of AOM recurrences
 - 3) Time-to-first AOM recurrence
 - 4) Proportion of AOM recurrences presenting with, respectively, intact bulging TM or tube otorrhea
 - 5) Total days per year subjects receive systemic antimicrobials for AOM
 - 6) Results of NP culture in children aged 6 to 23 months and of throat culture in children aged ≥ 24 months
 - 7) Direct medical costs, including payments to healthcare providers and the cost of medications used. First, at each study visit (every 8 weeks), we will ask parents about the number and type of encounters with healthcare providers (ED, hospitalizations, surgeries, ENT, primary care provider) and about antibiotic use. Cost of research-only visits will not be included in the calculation of the costs, except in cases where parents state that the visits prevented a visit for an otitis media-related concern. Second we will review each subject's medical records to ensure that all visits to health care professionals have been captured. We will separate costs into those related and unrelated to otitis media and its treatment. A clinician, masked to treatment assignment, will make this determination. This will allow us to compare both overall costs and costs specific to otitis media between the two treatment groups.
 - 8) Indirect medical costs: During study visits, information will be collected concerning the indirect costs of medical care associated with the occurrence of otitis media, including expenses related to travel for visits, alternate daycare expenses for the patient and/or siblings, as well as time costs (e.g., time for missed work).

11.5.3 Safety and Tolerability Assessments

Adverse events – During periods of antimicrobial therapy for AOM, parents will record in a diary complete information regarding (1) frequency and consistency of bowel movements in order to ascertain the incidence of PDD, which will be defined as the occurrence of ≥ 3

watery stools on 1 day or ≥ 2 watery stools on each of 2 consecutive days, (2) diaper rash necessitating administration of topical antifungal therapy, and (3) otorrhea.

11.5 Statistical Analysis

11.6.1 General Considerations

Study data will be monitored on an on-going basis by the Data Management and Statistical Unit in the Division of General Academic Pediatrics at Children's Hospital (DMSU) in Pittsburgh. The DMSU will inquire data clarification to the clinical sites for resolution while the study is on-going. Final cleaning and editing of the study database will be carried out after the last patient has completed follow-up. All changes to the study database will be documented. A permanent archive of the database will be maintained by the DMSU.

Primary analysis will be based on the intent-to-treat principle, with all data analyzed according to children's initial randomized assignment.

All statistical tests will be two-tailed and conducted at a significance level of 0.05. For the primary efficacy analysis, the significance level used will be determined taking into account any interim analyses for efficacy. For presentation, p-values will be rounded to two significant digits. If the first two digits are both 0 the value will be rounded to one significant digit or reported as "<0.001" as appropriate. All programs used in the statistical analysis of study data will be documented, tested, and archived. Archiving of statistical analyses at the DMSU includes the original written specifications for the analyses, any subsequent modifications, the computer program file, and the log, list, and other output files produced by the program. The DMSU will undertake all the analyses of study data, using the most current version of SAS®.

11.6.2 Interim Analysis

The external DSMB for the study will meet every 6 months. The DSMB will review patient enrollment and safety data at every meeting. One interim analysis for efficacy is planned after 120 children have been enrolled and completed follow-up. The interim analysis will include all patients whether or not they have completed the study. Type I error will be controlled by using the method of Fleming, Harrington and O'Brien⁶⁰ and testing will be conducted at two-sided significance levels of 0.005 and 0.048 at the interim and final analyses, respectively. If, at the interim analysis, the observed value of the test statistic comparing the average number of AOM episodes between the two treatment groups crosses the lower boundary of -2.81 favoring the TTP arm (efficacy monitoring) or crosses the upper boundary of 0.52 favoring the control arm at the interim analysis (futility monitoring),⁶¹ it may be advisable for the DSMB to consider disclosing the results. Here crossing the futility boundary implies that the accumulated evidence up to the 80% information point would start switching its direction toward superiority of the control arm.

For both safety and efficacy interim analyses, the DMSU will present the results for the two treatment groups to the DSMB. The DMSU's reports to the DSMB will include an open session focusing on enrollment, baseline characteristics and data completeness both by clinical site and overall, and a closed session where the interim safety and efficacy results will be presented according to treatment group. The closed session report will be seen only by the DSMB, key staff of the DMSU, and NIDCD personnel. At the end of each meeting, the DSMB will make a recommendation to NIDCD about continuing the study as planned, changing the design, or stopping.

11.6.3 Subject Disposition

Enrollment by study site and the number of subjects screened, randomized, withdrawn, and included in the analysis population (i.e. intent-to-treat [ITT]) will be reported for each treatment group. In addition, the number of subjects completing the study and the reasons for patient withdrawal will be tabulated by treatment group.

11.6.4 Baseline (Pre-Treatment) Analyses

Demographic and baseline clinical characteristics will be recorded for all patients by treatment group. For categorical variables, including gender, race/ethnicity, and concomitant medication use, frequencies and percentages will be reported. For continuous variables, including age, weight, and temperature, means and standard deviations will be reported.

11.6.5 Medication Use

The extent of concomitant medication use in the ITT population will be reported by treatment group.

11.6.6 Efficacy Analyses

Efficacy analyses will be based on comparisons between the TTP and nonsurgical management groups.

11.6.6.1 Primary Efficacy Analysis of the Primary Efficacy Endpoint

The primary outcome variable will be the rate of AOM episodes during the 2-year follow-up period. The Poisson regression model with the log-link function will be used to compare mean rates of AOM episodes between the two treatment groups, adjusting for the stratification variables. Wald tests will be used to assess the prognostic importance of each variable, and, if necessary, treatment-by-covariate interactions will be tested by adding interaction terms one at a time to the models.

As a sensitivity analysis, the primary outcome variable will be transformed to time to multiple events per subject. The frailty model⁶² will be applied to assess the treatment effect in reduction in the hazard ratio, adjusting for the correlation within subjects and stratification variables. We will also explore whether the duration of times that the tubes are in place could be used as a time-dependent covariate in this analysis.

11.6.6.2 Secondary Efficacy Analyses

Of the various secondary outcomes, we consider treatment failure as the most meaningful. Other secondary outcomes include categorical variables such as frequency distributions of AOM, time-to-event data, (e.g., time-to-first AOM recurrence), and continuous variables such as direct and indirect medical costs. For the categorical variables, a contingency table approach will be applied to compare two treatment groups. If a cell size is large, then a chi-squared approximation will be the test statistic. For binary variables, Fisher's exact test⁶³ will be used if at least one of the cell sizes is small. To adjust for confounding factors, the logistic regression model will be used. For the time-to-event data, the Kaplan-Meier method⁶⁴ will be used to estimate the survival probability in the presence of censoring in each treatment group. The log-rank test⁶⁵ will be used to test formally any differences in distribution between two treatment groups. The Cox's proportional hazards model⁶⁶ will be utilized to compare the hazard rates between two groups adjusting for stratification factors and other potentially confounding factors. For continuous variables, if the normality assumption holds, a two-sample t- or z-test will be used for the group comparisons, and a linear regression model will be used to adjust for confounding factors. If the normality assumption does not hold, appropriate nonparametric counterparts such as Wilcoxon-Mann-Whitney tests for two independent samples will be used. All assumptions required for the statistical models will be assessed including the proportional hazards assumption for Cox's model.

11.6.6.3 Statistical Analysis for Specific Aim 1

We hypothesize that TTP, compared with nonsurgical management, will reduce the average rate of AOM episodes during the 2-year follow-up period. We will compare mean rates of AOM episodes between the two treatment groups by applying the Poisson regression model with the log-link function. A total of 240 children with rAOM will be enrolled (See Section 11.6.8 for sample size justification). Secondly, estimates of change in mean rates of AOM episodes between the TTP and nonsurgical groups in the higher-risk and lower-risk children, respectively, will be useful in determining whether TTP is more beneficial for the subgroup of children at higher risk. The precision of these estimates will depend on the proportion of children assigned to the higher-risk stratum, as well as on the average number of episodes occurring in each risk subgroup. With the proposed sample estimate for the primary outcome (overall reduction) and assuming 25% attrition, if 40% of the children are at higher risk (based on our preliminary data in developing the rAOM-SRS), and if higher-risk children in the nonsurgical group have an average of 2 recurrences per year, we can estimate the difference in average number of

episodes between treatment groups within 0.84 episode with 95% confidence (secondary outcome); the corresponding estimate of the difference in lower-risk children is within 0.53 episode with 95% confidence (secondary outcome). As further extension of this secondary analysis, the treatment-by-risk group interaction will be formally tested.

11.6.6.4 Statistical Analysis for Specific Aim 2

Secondary hypotheses of interest for Specific Aim 2 relate to bacterial resistance. We wish to determine whether TTP compared with nonsurgical management is associated with a lower risk of NP colonization with resistant AOM pathogens. More specifically, the secondary analyses will include (1) the proportion of children whose NP cultures at randomization are, respectively, either negative for *S. pneumoniae* and *H. influenzae*, or positive for penicillin-susceptible pathogens, or positive for one or more penicillin-nonsusceptible pathogens, who subsequently are found on a follow-up NP culture to harbor one or more penicillin-nonsusceptible pathogens; (2) the proportion of interim, non-illness visits at which a penicillin-nonsusceptible pathogen is recovered; and (3) for all AOM episodes, the proportions of *S. pneumoniae* and *H. influenzae* isolates recovered at a visit during April or May (i.e. the end of the respiratory season) that are penicillin nonsusceptible. For hypotheses where the proportions of subjects with a specific characteristic are compared, we will assume a binomial distribution. When the summary statistic is the proportion of AOM episodes with a specific characteristic, we will assume episodes are clustered within an individual and adjust for correlations when making comparisons. To summarize resistance, we will use the conditional odds ratio (ORC) defined by Lipsitch et al.^{67,68} as the odds of having a resistant strain conditional on infection (or carriage) with that strain (both susceptible and resistant). This odds ratio addresses the question of community-wide effect of treatment on resistance as opposed to whether or not treatment makes the individual patient more likely to be colonized by a resistant organism. These comparisons will be made both (1) by randomized treatment group only, and additionally (2) by controlling for actual antibiotic use.

11.6.6.5 Statistical Analysis for Specific Aim 3

The first step will be to determine the differences in effectiveness and the differences in costs between the groups. We will use analysis of covariance to compare the average AOM-SOS scores at day 5 and day 12 in the two groups while adjusting for baseline values. The estimated difference in costs divided by the estimated difference in benefits will be our first estimate of the cost-effectiveness of TTP. We will then construct a decision analysis model comparing TTP and nonsurgical management. The probability of each outcome will be based on the probabilities observed in the trial. We will compare the performance of treatment strategies using the incremental cost-effectiveness ratio, defined as the extra cost of the more expensive strategy divided by its extra clinical benefit in QALYs. We will conduct one-way sensitivity analyses for all variables and two-way sensitivity analyses on selected variables in our model to assess the effect of varying baseline estimates within clinically plausible ranges of cost-effectiveness. Variables that change the results of the incremental cost-effectiveness ratio by more than 10%

in one-way sensitivity analyses will be selected for probabilistic sensitivity analyses, with parameters varied simultaneously over triangular probability distributions. Values from each probability distribution will be randomly selected during each of 10,000 Monte Carlo iterations. We will compute the percentage of Monte Carlo iterations for which a given strategy was more cost-effective for willingness-to-pay ceilings of \$100,000/QALY gained. Analysis will be conducted from a societal perspective using a 2-year time horizon. A power analysis for the cost effectiveness analysis would not be helpful since it involves knowledge of the joint distribution of the difference in costs and benefits between treatment groups, which usually introduces large variability.⁶⁹ Moreover, since we do not plan to use cost-effectiveness data for the purposes of inference, through probabilistic sensitivity analysis we will be estimating the likelihood that one strategy will be favored over others.

11.6.6.6 Missing Data

Study procedures aim to minimize missing data for the primary endpoint. If missing data occurs, the proportion of patients with missing data for the variable will be compared between the treatment groups and the sensitivity to the missing data will be examined by re-analyzing the outcome, and any substantial discrepancy will be fully investigated. We expect very few intervals with no observations prior to a patient's withdrawal from the study, so we will do no imputation for the few visits that are missed prior to a withdrawal. In the ITT analysis, we will compare the two treatment groups censoring patients at the time of withdrawal regardless of whether they have a functioning tube. However, we will perform a sensitivity analysis to investigate the impact of withdrawals on the outcome through multiple imputation where the covariate will include the number of recurrences of AOM prior to withdrawal. If a patient has missing data for a dichotomous secondary outcome variable, we will also perform a sensitivity analysis, first assuming that all such patients had a deleterious outcome and then assuming that all such patients had a favorable outcome.

11.6.6.7 Handling of Withdrawals/Crossovers

Subjects who are withdrawn from the study after randomization will not be replaced. Reasons for withdrawals will be summarized and reported. Over the course of the trial, children in the nonsurgical group might for one or another reason undergo TTP. These children will continue to be followed in the same fashion as those who completed the study without undergoing TTP. The occurrence of crossovers or withdrawals might lead to a loss of statistical power and/or potential bias. We have partially addressed the potential loss of statistical power due to the dropouts by increasing the sample size. In regard to bias, we will thoroughly investigate which factors are related to both withdrawals and crossovers. A secondary analysis will be performed by censoring patients in the TTP group at the time of tube removal if their tubes are removed and censoring patients in the antibiotics group if they undergo TTP. This will assess the pure effect of the surgical procedure and the results will be compared to the previous ITT analysis.

11.6.7 Safety and Tolerability Analyses

11.6.7.1 Adverse Events

During periods of antimicrobial therapy for AOM, parents will record in a diary complete information regarding (1) frequency and consistency of bowel movements in order to ascertain the incidence of PDD, which will be defined as the occurrence of ≥ 3 watery stools on 1 day or ≥ 2 watery stools on each of 2 consecutive days, (2) diaper rash necessitating administration of topical antifungal therapy, and (3) otorrhea.

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject who is administered a pharmaceutical product, regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

We will track (1) common or important adverse events potentially linked to the study-related therapies (e.g., PDD, generalized rash); (2) severe adverse events that require more than minimal medical intervention (see below); and (3) serious adverse events (see section 9.2.3).

The occurrence of AEs will be recorded from Day 1 (enrollment) through the end-of-study visit. AEs will be documented regardless of relationship with clinical antibiotic treatment or study intervention. All recorded AEs will be followed to adequate resolution. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases at any time during the study, it may be recorded as an AE. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

AEs will be classified as follows:

Mild: events require minimal or no treatment and do not interfere with the subject's daily activities.

- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- Severe: events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Examples of the types of AEs that will be collected (contained within the heavy lines) and of AEs that will not be collected (gray font and marked by an asterisk), are shown in the Table below.

** Otorrhea within 7 days of TTP will not be considered an adverse event

Categories of Adverse Events			
	Mild	Moderate	Severe
Rash	*Localized rash or slight pruritus	Generalized, moderate pruritus	Generalized severe urticaria; serum sickness; Stevens-Johnson Syndrome
Diarrhea	*Loose stools	3 or more watery stools in 1 day or 2 watery stool daily for at least 2 days (i.e., PDD)	Diarrhea requiring rehydration therapy and is incapacitating
Otorrhea**	*<7 days requiring treatment with topical antibiotics	≥7 days requiring the addition of oral antibiotics and culture-directed therapy	Caused by resistant bacteria requiring intravenous antibiotics
All other Adverse Events	*Requires minimal or no treatment and does not interfere with daily activities	*Requires some treatment and may interfere with daily activities	Requires systemic drug therapy and is clearly incapacitating

Relationship to clinical antibiotic treatment or study intervention (TTP): The study clinician's assessment of an AE's relationship is required prior to any unmasking. Factors that will be considered in determining a causal relationship include whether: (1) the event is described in the product insert; (2) a temporal relationship exists between the event and the administration of clinical antibiotic treatment or study intervention (TTP); (3) a possible alternative etiology has been identified; and (4) it is biologically plausible that the event may be related. To help address this issue, the following guidelines are used:

- **Related** – There is a reasonable possibility that clinical antibiotic treatment or study intervention (TTP) caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the clinical antibiotic treatment or study intervention and the adverse event.
- **Not Related** – There is not a reasonable possibility that clinical antibiotic treatment or study intervention (TTP) caused the event.

11.6.7.2 Resource utilization

We will collect data on direct costs (i.e., visits to healthcare providers; medications) and indirect medical costs. For direct costs, we will ask parents about the number and type of encounters with healthcare providers since enrollment in the study and between study visits. Similarly the number and types of medication used will be ascertained. For indirect costs, we will collect information on the costs associated with the diagnosis of AOM, including travel expenses, alternate child care expenses for the patient and/or siblings, as well as time costs (e.g., for missed work). These assessments will be conducted at the time of the follow-up visit.

11.7.1 Sample Size Justification

Hypothesizing that TTP, compared with nonsurgical management, will reduce the average number of AOM episodes during the 2-year follow-up period, mean rates of AOM recurrences will be compared between the two treatment groups by assuming a Poisson distribution. A total of 240 children with rAOM will be required. This number will permit, with a two-sided significance level of 0.05 and power >.90, detection of a 33% reduction in the average number of AOM recurrences in the surgical group, assuming that children receiving nonsurgical management will have an average of 1.5 episodes per year and estimating 25% attrition over a 2-year period. The increase in sample size to account for dropouts is conservative in regard to preserving statistical power since withdrawals will still contribute some follow-up data to the analysis. However, it might not adjust for loss of power due to crossovers or for potential bias due to differential withdrawal patterns in the two treatment arms. (See Section 11.6.6.7)

The Table shows the statistical powers achieved in addressing the primary hypothesis in

No. children enrolled per arm = 120				
No. of AOM recurrences during 2-year follow-up in nonsurgical arm	Number of children evaluable per arm (attrition)			
	90 (25%)	84 (30%)	78 (35%)	72 (40%)
	Power			
2.0	.90	.88	.85	.82
2.5	.96	.94	.93	.90
3.0	.98	.97	.96	.95
3.5	.99	.99	.98	.97

Specific Aim 1 for various estimates of the number of AOM recurrences in the nonsurgical arm and different attrition rates.

Table 1. Power estimates for finding a 33% reduction in the number of AOM recurrences in children undergoing TTP, with enrollment of 120 children according to baseline recurrence rates in the nonsurgical management arm and varying levels of attrition.

6.9 Data management and quality control

See Manual of Procedures.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating clinical study site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating clinical study site will permit authorized representatives of NIDCD, University of Pittsburgh, and applicable regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data. CHP and CNMC use certified, comprehensive EHR systems requiring privacy and security compliance and HIPAA and institutional policies addressing unauthorized access to the EHR systems; these policies preclude external representatives listed in this protocol from accessing the EHR. However, paper copies of the respective EHR system documentation may be provided to the monitors for review.

Source data are all original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, TM images and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The eCRFs provided by the DCC at the University of Pittsburgh Center for Research on Health Care will be source documents. Information about each subject's pertinent history, treatment, clinical findings, TM images, and results of laboratory tests will be entered into the eCRF, which will be the source document for most of the data collected in this study. Additional source documents include the patient's medical record (i.e., utilization of health care resources), parent/legal guardian memory aid, and laboratory reports (received directly from the Micro lab and entered into the eCRF). Clinical data (including AE/SAEs, concomitant medications, physical assessments, memory aid information, otoscopic findings, and TM images) and laboratory data (including NP swab specimen cultures) will be entered into a 21 CFR Part 11-compliant Internet eCRF provided by the University of Pittsburgh Center for Research on Health Care. Clinical and laboratory data will be entered directly from the source documents or during the parent/legal guardian interview.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigators will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997). Each investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by OHRP for federally funded research.

Each participating clinical study site investigator will choose subjects in accordance with the eligibility criteria detailed in Section 5. The investigator will not exercise selectivity so that bias is prevented.

13.2 Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and the informed consent form will be reviewed and approved by the appropriate institutional review board (IRB) listed on their FWA.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to NIDCD. The IRB Federal Wide Assurance number will be provided to NIDCD.

Any amendments to the protocol or informed consent form will be approved before they are placed into use and a copy of the signed IRB letter of approval will be provided to NIDCD.

The University of Pittsburgh Institutional Review Board (for CHP and Pediatric PittNet) and CNMC IRB (for both CNMC and CP&A), both registered with OHRP, will review and approve the protocol and informed consent form prior to commencement of subject recruitment.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the subject's parent/legal guardian agreeing to have their child participate in the study, with agreement continuing throughout the subject's study participation. Extensive discussion of risks and possible benefits of this therapy, and of the concept of placebo, will be provided to the subject's parent/legal guardian. Consent forms describing in detail the study intervention, study procedures and risks will be given to the subject's parent/legal guardian and written documentation of informed consent will be obtained. Consent forms will be IRB-approved and parent/legal guardian of subjects will be asked to read and review the document. Upon reviewing the document, the investigator will explain the

research study to the subject's parent/legal guardian and answer any questions that may arise. The parent/legal guardian may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subject's parent/legal guardian for their records. The rights and welfare of the subjects will be protected by emphasizing to the parent/legal guardian that the quality of their child's medical care will not be adversely affected if they decline to have their child participate in this study.

All subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

Subjects in this study are between the ages of 6 and 35 months and therefore will not be able to provide assent.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

The study will be conducted in children aged 6 to 35 months (inclusive), an age group that experiences the highest incidence of AOM. As all study participants will be children, we anticipate an adequate number of subjects in this age group to contribute to a meaningful analysis. Children who meet eligibility criteria as detailed in Section 5 will be entered in the proposed study without regard to sex, religion, or ethnic background and it is anticipated that enrollees will be divided approximately equally between boys and girls. We will recruit and enroll children who are representative of the sex, racial, and ethnic distribution of patients with AOM at the participating clinical study sites. No subject will be included or excluded on the basis of sex, race or ethnicity. Self-reporting of ethnicity and race using two separate questions will be used to identify demographic information as required by OMB Directive 15.

13.5 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the investigators, their study personnel, the sponsor(s) and their agents. This confidentiality will be extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the sponsor and all data and information generated by the participating clinical study sites as part of the study (other than a subject's medical records) will be kept confidential by the investigators and their study personnel. This information and data will not be used by the investigators or their study personnel for any purpose other than conducting

the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigators or their study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the study; (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 17. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating clinical study sites will permit access to such records.

All study data will be stored in locked file cabinets and kept in the respective research areas at each participating clinical study site. All paper records containing identifying information will be kept in locked files accessible only to the investigators and their study personnel and unlocked only while study personnel are working with the files. To ensure that confidentiality is maintained, the study coordinator will conduct inspections of the relevant premises at random times, usually weekly. Information regarding individual subjects will be kept private and shared only with the IRB, DSMB, the investigators, their study personnel, and the sponsor(s) and their agents. Primary care providers will be informed about their patient's progress periodically and will be notified if problems in management occur.

Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant Internet eCRF provided by the University of Pittsburgh Center for Research on Health Care. The data management system includes password protection, automatic time/date stamp and internal quality checks, such as automatic range checks that occur in real time to identify data that appear inconsistent, incomplete, or inaccurate. At CHP, Pediatric PittNet practices, CNMC, and CP&A, the respective information technology departments will take all necessary steps to protect the confidentiality, integrity, and availability of all information assets on the computer network from unauthorized access, while providing mechanisms to grant, monitor, modify and remove access, as required. At CHP, for example, users are authorized to access CHP's IT resources based on roles and responsibilities necessary to perform the functions of their jobs. Access will be granted based on what is minimally necessary for job completion. At all sites, computer user accounts and passwords will be used to uniquely identify and authenticate a user to a computer system or application. Accessing a computer application or system with a username and password will be considered equivalent to the user's signature.

Additional efforts at the DCC include limiting access to areas containing electronic confidential information. This includes monitoring the movement of people, equipment, and supplies into or out of the areas containing confidential information. The DCC requires card access or pre-approved visitor sign-in. Physical controls for the data center include:

- Locked doors with restricted, logged, card key access

- Video surveillance monitored by security and public safety personnel
- Raised floor
- Heat, smoke, and water detection
- Environmental controls for heat and humidity
- Fire suppression
- Supporting utilities monitored by facilities personnel

Further, the DCC's network is protected via an intrusion detection system (Solutionary) that protects against malicious code, denial of service attacks and viruses. Interception of data transmission and electromagnetic interception are addressed by domain-based policies that manage data securely with security standards of IPsec, VPN, SSH, and PGP encryption.

Computers at each participating clinical study site must be compliant with CHP standards to be granted access to the system. All participating study site computers must be protected by an institutional firewall or local firewall software. Each computer must also be protected by local anti-virus and anti-spam software. These standards are verified through an authorization process overseen by the DCC and CHP. At each participating study site, each protocol team member shall be assigned only one unique account for each computer system or application. Passwords shall consist of seven or more characters and contain characters from three of the following four categories: capital letters (A through Z); lowercase letters (a through z); numbers (0 through 9); and symbols (!, \$, #, %, @). Computer systems or applications shall automatically inform the account holder when a password change is required. New computer accounts shall be created with a one-time password that requires the user to establish a unique password during the initial log on.

In the event that a breach is suspected of any system, administrative, or user account, all potentially compromised account passwords shall be immediately changed, and the appropriate help desk shall be notified to investigate the potential security breach.

To protect against data loss, each participating clinical study site will adhere to the DCC and CHP data backup and recovery plans, which include procedures for creating and maintaining retrievable exact copies of information, programs, and operating systems. The plan includes:

- Regular back-ups
- Secure off-site storage of tapes and documentation
- Regular testing of backup media
- Incident response procedures

- Disaster recovery plans with procedures for restoring lost information
- Emergency mode of operation plan that contains procedures protecting electronic information while operating in an emergency situation
- Testing and revision plan that contains procedures for periodic testing and for revisions of the contingency plans that may be necessary or advisable..

Any publications or presentations resulting from this work will not identify participants by name, but will present only aggregate data.

13.6 Costs, Subject Compensation, Research Related Injuries

There will be no costs to the subject or their parent/legal guardian for participation in this study. Subjects' parents/legal guardians may be compensated for participation in this study. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval. Parents/legal guardians will be reimbursed at each visit for their time and expenses, according to the local standards and IRB approval.

When needed, based on time of the year and climate conditions, taxicabs or "gas cards" may be used to facilitate transportation. Parents will receive free parking for each study visit, as applicable per site,

Parents/legal guardians will be encouraged to immediately contact the Principal Investigator if they believe that the research procedures have resulted in an injury to their child. Emergency medical treatment for injuries solely and directly related to participation in this research study will be provided to participants. The insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to the participant. If the research-related injury requires medical care beyond this emergency treatment, parents/legal guardians will be responsible for the costs of this follow-up care. No plan exists for any additional financial compensation.

13.7 Study Discontinuation

In the event that the study is discontinued, enrolled subjects will continue to be followed for safety assessments. Enrolled subjects will also be referred to their physician for further follow-up.

13.8 Future Use of Stored Specimens

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

The investigators are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

The eCRF will be developed by the DCC as the source document to record and maintain data for each subject enrolled in the study. Data reported in the eCRF should also be consistent with other source documents (memory aid or other places where data could potentially be first recorded), or the discrepancies should be explained.

Any other source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, the original entry will be crossed with a single line, initialed and dated, without obliterating the original entry. The DCC will provide guidance to investigators on making corrections to the eCRF or other source documents.

14.1 Data Management Responsibilities

All source documents will be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. All memory aids will be reviewed with the parent at the time of the visit to clarify any questions about items entered. Adverse events will be assessed for severity and causality, and reviewed by the participating clinical study site investigator or designee.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site investigator. During the study, the investigators must maintain complete and accurate documentation for the study.

The University of Pittsburgh Center for Research on Health Care will serve as the DCC for this study and will be responsible for data management, quality review, analysis, and reporting of the study data, including uploading results to the National Library of Medicine (NLM) database. The DCC will manage data by developing checks on the central database for logical inconsistencies and reports for the participating clinical study sites, including recruitment, retention, missing forms, subject follow-up visit schedules, and treatment adherence.

The DCC can generate reports, including data quality and compliance information. Information on form submission and completeness will be available through the central database. Information will also be available to chart protocol progress, including recruitment and retention, schedule of upcoming patient visits, and quality of the data obtained. Other specialized reports may also be developed.

Study personnel can query data from the central database in real-time and generate customized reports displaying current data for their clinical study site. NIDCD will be provided with read-only

access to the central database in real time. If necessary, study, data entry, and management personnel can view the same information simultaneously when troubleshooting a data issue.

14.2 Data Capture Methods

Screening logs of eligible and enrolled subjects will be maintained to detect the possibility of selection bias. The University of Pittsburgh Center for Research on Health Care eCRF will be accessible from participating clinical study sites using a secure Internet connection. The data management system will present study site personnel with a readily available and comprehensive set of data management tools to perform data entry and routine processes, by displaying information regarding forms that have been received, forms that are due, and forms that are late. The eCRF incorporates automatic edit checks that serve to prevent errors and substantially reduce time to clean data. The eCRF permits capture and transmission of TM images, which will enable clinicians at participating clinical study sites to discuss otoscopic findings as needed with the investigators via computer or cellular phone, further enhancing the accuracy of both diagnosis and classification of treatment outcome.

Information about each subject's pertinent history, treatment, clinical findings, TM images, and results of laboratory tests will be entered into the eCRF, which will be the source document for most of the data collected in this study. Microbiologic information related to results of NP swabs will be entered into the eCRF at the Infectious Diseases Research Laboratory. The memory aid will also be a source document from which information will be abstracted into the eCRF. Very limited additional information may need to be gathered from the EHR, in particular, as it relates to utilization of healthcare resources or adverse events. Clinical data (including AE/SAEs, concomitant medications, physical assessments, memory aid information, otoscopic findings, and TM images) and laboratory data (including NP swab specimen cultures) will be entered into a 21 CFR Part 11-compliant Internet eCRF provided by the University of Pittsburgh Center for Research on Health Care. The data management system includes password protection, automatic time/date stamp and internal quality checks, such as automatic range checks that occur in real time to identify data that appear inconsistent, incomplete or inaccurate. Clinical and laboratory data will be entered directly from the source documents or during the parent/legal guardian interview. This will allow for ongoing and rapid query resolution and locking of the database at the close of the study.

14.3 Types of Data

Data for this study will include safety, laboratory and outcome measure information gathered in the eCRF (medical history, demographics, concomitant medications, ear examination findings (otoscopic findings), physical examination findings, laboratory results (NP swab specimen cultures), records of medical encounters at other facilities (if needed to document adverse events; appropriate permission forms will be obtained), and images of TMs. It will also include information gathered in a parent/legal guardian memory aid concerning signs and symptoms of

AOM (AOM-SOS scale). Other data include level of parental satisfaction and utilization of healthcare.

14.4 Timing/Reports

Study data will be reviewed by the DSMB per the DSMB charter for this study. Interim statistical reports may be generated as deemed necessary and appropriate by NIDCD. An Interim Report for DSMB review will be prepared by the DSMU after 120 subjects have been enrolled and completed follow-up. The DSMB may receive data in aggregate and presented by treatment group assignment, but without the treatment group assignment identified. The DSMB may be unblinded to treatment group assignment, as needed, to assess safety issues. As an outcome of each review and meeting, the DSMB will make a recommendation at that time as to the advisability of continuing, modifying or terminating the study.

Reports to the DSMB -- In general, the DMSU will prepare reports as directed by the DSMB and NIDCD. The contents of the reports will be determined by the DSMB and NIDCD. Additions and other modifications to these reports may be directed by the DSMB and/or NIDCD. These reports will contain the most up-to-date data permitted by the timeframe necessary for the DMSU to prepare and review the analyses. Reports will usually consist of two parts, corresponding to the open and closed sessions of the DSMB meeting, and include an assessment of the progress of the trial, including recommendations on whether it should continue or be terminated or modified. Only the DSMB members will receive copies of the closed session report. The reports will be sent by the DMSU to the NIDCD DSMB support contractor for distribution to the DSMB members and NIDCD at least 14 business days prior to a scheduled meeting. An Interim Report will be prepared by the DMSU after 120 subjects have been enrolled and completed follow-up.

14.5 Study Records Retention

Study documents (records and documents pertaining to the conduct of this trial, including eCRFs, memory aides, consent forms, and laboratory test results) will be retained for a minimum of 5 years in compliance with the rules of the University of Pittsburgh, for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records will not be destroyed without the permission of NIDCD. Since this research involves children, all research records will be maintained until the youngest participants have reached the age of 23.

14.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the subject, the parent/guardian,

the investigators, or study personnel. As a result of deviations, corrective actions will be developed by the participating clinical study site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It will be the responsibility of the participating clinical study site to use continuous vigilance to identify and report deviations to NIDCD via email and to the IRB per their guidelines. All deviations will be reported to NIDCD and ISMs on a monthly basis. Deviations will also be included in the DSMB reports.

All deviations from the protocol will be addressed in study subject source documents. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the subject's source document. The investigators and their study personnel are responsible for knowing and adhering to their IRB/IEC requirements.

15 PUBLICATION POLICY

Following completion of the study, the principal investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- <http://publicaccess.nih.gov/>
- <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html>

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

For trials in which NIDCD is not the IND/IDE sponsor, or there is no IND/IDE, and NIDCD does not provide data management services, it will be the responsibility of the principal investigator as the "Responsible Party" to register the trial and post results in compliance with Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA).

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases

It is the responsibility of the principal investigator to register this trial in an acceptable registry.

[De Angelis C](#), [Drazen JM](#), [Frizelle FA](#), [Haug C](#), [Hoey J](#), [Horton R](#), et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004;351:1250-1.

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

	Screen Part 1		Randomization Part 2															
Evaluation	Entry	Sick visit	Entry	Q 8-week visits													Sick visit	
				1	2	3	4	5	6	7	8	9	10	11	12	1 3		
Inclusion/ exclusion	X		X															
Informed consent	X		X															
History	X		X															
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs Weight*		X	X														X	
Randomization			X															
Clinical signs and symptoms			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pneumatic otoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NP or throat culture†			X		X		X		X		X		X		X	X	X	
TM image‡	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AOM-SOS §	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Parent questionnaires			X		X		X		X		X		X		X	X	X	

*Vital signs/weight - as clinically indicated

†Nasopharyngeal or throat swab – indicated by age of participant

‡TM image – if available when AOM dx and sometimes with normal dx

§AOM-SOS scale

APPENDIX B: AOM-SOS SCALE (VERSION 4.0)

How has your child been doing?

We are interested in finding out how your child has been doing. For each question, please place a check (✓) in the box corresponding to your child's symptoms. Please answer all questions.

	No	A Little	A Lot
Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Over the past 12 h, has your child been crying more than usual?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Over the past 12 h, has your child been more irritable or fussy than usual?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Over the past 12 h, has your child been having more difficulty sleeping than usual?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Over the past 12 h, has your child been having fever or feeling warm to touch?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Thank you