Evidence-based Practice Center Systematic Review Protocol

Project Title: Otitis Media With Effusion: Comparative Effectiveness of Treatments

Amendment Date(s) if applicable: July 30, 2012

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Otitis media with effusion (OME) is defined as a collection of fluid in the middle ear without signs or symptoms of ear infection.[1] It typically arises when the Eustachian tubes are not functioning normally. When this happens, pressure changes occur in the middle ear and fluid can accumulate.

OME is one of the most commonly occurring childhood illnesses in the United States with more than 2.2 million diagnosed cases each year at an estimated annual cost of 4 billion dollars.[2] As many as 90 percent of children (80% of individual ears) will have at least one episode of OME by age 10, with the majority of cases occurring between the ages of 6 months and 4 years.[2, 3] Many episodes of OME resolve spontaneously within 3 months, but 30 to 40 percent of children have recurrent episodes and 5 to 10 percent of cases last more than 1 year.[1, 4, 5] Additionally, some subpopulations of children are disproportionately affected by OME. Those with cleft palate, Down syndrome, and other craniofacial anomalies are at high risk for anatomic causes of OME in addition to worsened function of the Eustachian tube.[6] Individuals of American Indian, Alaskan, and Asian backgrounds are believed to be at greater risk,[7] as are children with adenoid hyperplasia. In addition, children with existing hearing loss will be affected more dramatically by the secondary conductive hearing loss that occurs with OME.

There are several predisposing environmental factors that are associated with an increased risk of developing OME.[3] These include exposure to secondhand smoke, attending child care, and having environmentally induced allergies.

Although rare, OME also occurs in adults, usually developing after a severe upper respiratory infection such as sinusitis, severe allergies, or rapid change in air pressure (barotrauma) after a plane flight or a scuba dive. The incidence of prolonged OME in adults is not known, but it is much less common than in children.[8]

OME can be associated with discomfort and a feeling of fullness in the ear. Patients with OME are also prone to episodes of acute otitis media (AOM). Temporary hearing loss is common among OME

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patients. This hearing loss is often mild (i.e., worsened or with hearing threshold elevated by about 10 dB), but in some cases moderate or severe hearing loss can occur.[9] Because hearing loss in young children may delay or permanently change their communication skills and may lead to behavioral and educational difficulties,[10] there has been concern about the possible role of OME on these outcomes. Additionally, those with chronic Eustachian tube dysfunction and OME are at risk for structural damage of the tympanic membrane.[11]

Taking a careful history is important to identify risk factors for developing OME. For example, it can be helpful to elicit a history of recent upper respiratory infection, allergy, subjective hearing loss or imbalance, speech and language delay, and a history of cleft palate or Down syndrome.

Diagnostically, OME must be first identified and then distinguished from AOM. OME is diagnosed with the presence of fluid behind the tympanic membrane, without acute onset or signs of inflammation or infection. AOM on the other hand, while it may include Eustachian tube dysfunction and middle ear fluid, it must include signs of acute inflammation or infection. Another distinguishing feature between AOM and OME is the appearance of the tympanic membrane, which bulges with AOM and is typically retracted or neutral with OME. With OME, the tympanic membrane is often cloudy with impaired mobility. Additionally, an air-fluid level or bubble(s) may be visible in the middle ear.[10] The use of pneumatic otoscopy to demonstrate decreased mobility of the tympanic membrane is considered an important primary diagnostic method.[1] Other factors that help confirm the diagnosis include a flat tympanogram (Type B tympanogram) and a conductive hearing loss on pure-tone audiometry. Hearing is generally measured across the speech range, and for young children normal hearing is considered to be no worse than 15 dB (which is the measure of loudness needed to respond to a sound).[12] In contrast, the average hearing levels for ears with OME often measure at 25 dB, with about 20 percent exceeding 35 dB.[1] Though usually not necessary to make a diagnosis, middle ear effusion can be demonstrated on imaging studies, such as computed tomography (CT) of the temporal bone.

Tympanocentesis (use of a needle to puncture the tympanic membrane to allow for fluid drainage, aeration), usually performed at the time of myringotomy with or without tympanostomy tube placement, remains the gold standard for diagnosing OME. While AOM may also present with fluid behind the tympanic membrane, it is defined as also including an acute onset of signs and symptoms of middle-ear inflammation.[10]

Given the natural history of OME, particularly in relation to the high instance of spontaneous resolution, clinical decisions are complicated, and despite recent practice guidelines and systematic reviews,[6, 10, 13-19] the comparative benefits and harms of treatments and treatment strategies for OME are uncertain.

Table 1 lists the various surgical and non-surgical treatments and overall strategies for treating OME. During topic refinement, we looked at each treatment in terms of uncertainty within the published literature (including gaps in the evidence), clinical importance, patient important outcomes, and relevance to the U.S. population.

Table 1. Interventions and treatment strategies for otitis media with effusion

Surgical Interventions
Myringotomy
Tympanostomy tubes
Adenoidectomy with or without myringotomy
Pharmacological Interventions
Antibiotics and antimicrobials
Nasal steroids
Oral steroids
Antihistamine and decongestants
Nonsurgical and Nonpharmacological Interventions
Autoinflation of the Eustachian tube
Complementary and alternative therapies
Hearing aids
Treatment Strategies
Watchful waiting/delayed treatment/immediate treatment
Variations in surgical technique and procedures

Treatments That Will Not Be Addressed in This Review: Rationale for Exclusion

The use of **antihistamines and decongestants** for the treatment of OME has been extensively studied in primary randomized controlled trials (RCTs) and summarized in recent systematic reviews[19, 20] and clinical practice guidelines.[6, 10] A Cochrane review of OME for use in children identified 16 RCTs that included over 1,800 subjects.[19] The effects on multiple short- and long-term outcomes repeatedly demonstrated no benefit for use of these medications over placebo for treating OME. Additionally, the reviewed studies found evidence of increased side effects and harms with the use of these medications. High-quality evidence unequivocally demonstrates that antihistamines and decongestants offer no improvement over placebo, and there is no reason to believe that this will change with future advances in the medication class or causes of OME. We have, therefore, decided to exclude antihistamines and decongestants from the current review as a treatment that is definitively not effective and likely harmful.

Antibiotics currently are not commonly used in the United States to treat OME and are not recommended in current U.S. guidelines.[10] There is some conflicting evidence regarding the effectiveness

and utility of antibiotics for the treatment of OME.[6, 10, 20] An upcoming Cochrane Collaboration review on the use of antibiotics for the treatment of OME in children was started in 2011 and is well underway.[21] We will not duplicate their efforts and have excluded antibiotics from the current comparative review.

Hearing aids are not used as a treatment option for OME in the United States and, according to a 2008 National Collaborating Centre for Women's and Children's Health (NICE) guideline,[6] there are no high-quality comparative studies evaluating the effectiveness of hearing aids to other interventions for treating OME. Furthermore, we did not find any comparative studies on hearing aids during topic refinement, and our Key Informants did not consider hearing aids of clinical relevance in the context of OME. Hearing aids, therefore, will not be included in the current review.

Treatments and Treatment Strategies That Will Be Addressed in This Review: Rationale for inclusion

The benefits and harms of **oral and topical nasal steroids** in treating hearing loss in children with OME was the focus of a recent Cochrane Collaboration review (2006).[18] The review was limited to RCTs identified through May 2006, of either steroid use alone or in combination with another agent such as antibiotics, and included special populations of children of interest to our current review. Oral steroids alone or in combination with antibiotics had a positive effect on 2-week disease outcomes but not on longer term outcomes. Topical nasal steroids were also found to have a minimal effect in treating OME in two included studies. Current guidelines developed by both the United Kingdom's National Collaborating Centre for Women's and Children's Health (2008)[6] and the American Academy of Pediatrics (2004)[10] recommend against using oral or topical nasal steroids in treating children with OME. For the purposes of identifying the relevant literature for this review, we assume that the Cochrane Collaboration review identified all relevant RCTs as of the time of their review. We will search the published literature for studies on treating OME with either oral or topical nasal steroids in children and will only consider re-reviewing this intervention if we find new evidence, RCTs published in May 2005 or later (1 year before the last literature search in the Cochrane review), or observational studies from any time. In consultation with our Technical Expert Panel (TEP), we conclude that it would be useful to integrate newly identified studies with those previously identified through the Cochrane Collaboration review, because the newly integrated studies may result in conclusions different from those of the earlier review.[18] We will conduct a completely new search to identify studies pertaining to adults, because we did not find an existing review focusing on this population.

Adenoidectomy as a treatment for OME in children has also been recently reviewed in a 2010 Cochrane Collaboration systematic review.[16] The review included seven RCTs comparing adenoidectomy (with or without tympanostomy tubes) and nonsurgical management or tympanostomy tubes only; studies of children up to 18 years of age; followup of 6 months or longer; and not limited to otherwise healthy children. Our search strategy will be to assume that this Cochrane 2010 review[16] identified all relevant studies relating to both special populations and otherwise healthy children in the literature at the time of the review. We will search for RCTs published in March 2008 forward (1 year before the end of the earlier search) and observational studies from any time. We are not aware of any reviews of adenoidectomy in adults with OME; therefore, we will search the literature to locate any relevant studies.

Though not in widespread use, the technique of **autoinflation** has been used as a treatment for OME. The goal of autoinflation is to use either a Valsalva maneuver or external device to equalize middle ear and oropharyngeal pressure, essentially transiently opening the Eustachian tube. A 2006 Cochrane Collaboration study included six RCTs examining the use of autoinflation versus no treatment for hearing loss associated with OME.[17] Studies included children, adults, and special populations and concluded that the evidence for the use of autoinflation in the short term was favorable; however, given the small number of studies and lack of long-term followup, the long-term effects could not be determined. We will begin with the studies identified in the 2006 Cochrane review and will search for new RCTs published since August 2005 (1 year before the last search conducted for the 2006 Cochrane review) and observational studies published at any time. We will newly synthesize the literature related to this intervention if we determine that there are sufficient data to examine the efficacy of autoinflation in subpopulations and/or the comparative effectiveness of autoinflation relative to other treatment options.

There is a literature on **complementary and alternative medicine (CAM) interventions** to treat OME. The book *Evidence-Based Otitis Media*[22] lists treatments and supportive studies for at least two CAM approaches including physical manipulation and restricted diets. Based on the recommendations of our TEP, in the current review we will only include RCTs of CAM interventions.

Although the most recent guidelines for treating OME do not recommend the use of **myringotomy** alone,[10] more recent literature suggests that laser-assisted myringotomy may be a useful alternative to myringotomy plus tympanostomy tubes. These recent studies suggest that it may provide a treatment with fewer complications for selected subgroups of children and adults.[23-26] Because there have been no systematic reviews that have addressed the effectiveness of myringotomy alone, we will search for relevant RCTs and observational studies examining myringotomy alone as a treatment strategy for OME in otherwise healthy children, special populations of children, and adults.

The harms and benefits of **tympanostomy tubes** for managing OME in children have been addressed by two recent systematic reviews.[13, 15] A 2010 Cochrane review of 10 RCTs,[15] limited to otherwise healthy children, concluded that tubes are beneficial for the outcome of hearing in the short term, but the size of the benefit diminishes after 6 to 9 months with no differences seen at 12 and 18 months. With limited data available, no effects were detected on language or speech development or cognitive or quality-of-life outcomes. At least five of the included studies considered long-term outcomes, following children 8 years postsurgery. A 2011 systematic review, commissioned by the Swedish Council on Technology Assessment in Health Care,[13] looked at tympanostomy tubes as a treatment for OME, not excluding special populations of children. Based on eight RCTs that followed children for as long as 10 years, the review concluded that there was strong evidence that tympanostomy tubes improve hearing and quality of life in the short term (up to 9 months). Comparators included no treatment, watchful waiting, and other established treatments. For this review, we will begin with the RCTs that were identified in both of these earlier systematic reviews and will search for new RCTs from April 2006 forward (1 year before the last search that included all children) and observational studies from any time. In addition, we will search for relevant studies in the adult population.

A growing body of literature examines variations in tympanostomy tube-related surgical techniques and procedures for treating OME. The 2011 Swedish systematic review described above[13] considered

various characteristics of tube design and surgical procedures and concluded that there is as yet insufficient evidence to determine if the design of the tube material or variations of surgical procedure has an impact on function. We will search from April 2006 forward (1 year before the last search of the Swedish systematic review) for relevant studies comparing tympanostomy tube materials, designs, and surgical procedures.

Watchful waiting, or active observation as it has more recently been called, is the process of regular review and followup of the child, including assessments of hearing, development, and educational progress. We will examine this as a treatment strategy, distinct from "no treatment." Watchful waiting has not been the focus of a systematic review, although it has been a comparator in RCTs included in systematic reviews focusing on other interventions. Current clinical practice guidelines recommend that watchful waiting be employed for 3 months in otherwise healthy children.[6, 10] We will search for relevant RCTs and observational studies that examined watchful waiting as a treatment strategy for OME in otherwise healthy children, special populations of children, and adults.

We have considered whether to include studies reporting outcomes by ears, rather than by subjects. Exclusion of studies by ears is reasonable and appropriate when: 1) the treatment involved is systemic, or 2) outcomes are measures of the patient's overall function, such as academic achievement, speech production, language development, or quality of life. For ear-specific treatments or outcomes such as hearing thresholds or presence of fluid, ear-specific reports will be included in this current review.

II. The Key Questions

Proposed Key Questions (KQ)s were posted for public comment and the following concerns were expressed:

1. Differences between KQs 1 and 2 are insufficient to justify two questions.
2. In KQ 5, health insurance coverage is not a health care–delivery characteristic, rather an enabler of health care delivery and therefore inappropriately included in a list of health care–delivery characteristics.
3. Geographic location and home environments were not included in the list of health care characteristics in KQ 5.

After consulting with our Task Order Officer, we respond to each of these comments as follows:

1. We will keep KQs 1 and 2 as separate questions to clearly distinguish between clinical outcomes and function and quality-of-life outcomes. We believe that this is appropriate because studies have shown that clinically measured outcome levels may not parallel the patient's or parent's perceptions of functionality. For example, the presence of middle ear fluid does not necessarily result in a perception of reduced hearing.
2. In KQ 5, to eliminate confusion about the appropriate categorization of health insurance coverage, we have eliminated the phrase "health care-delivery characteristics." Outcome

differences that can be attributed to health insurance are retained as one of the factors that will be considered.

3. In KQ 5, we have clarified that location of the treatment provider is more accurately described as "type of facility of the treatment provider" and have added "geographic location" as a factor that may affect treatment outcomes. We have not added "home environment" as this concept is vague and difficult to define in relation to its potential effect on treatment outcomes.

4. In KQ5, we have replaced the word "modified" with "affected" to encompass the potential of the factors either modifying or mediating treatment outcomes.

The revised and finalized KQs following public comment are below. PICOTS were not affected by these changes in the KQs.

KQ 1: What is the comparative effectiveness of the following treatment options (active treatments and watchful waiting) in affecting clinical outcomes or health care utilization in patients with OME? Clinical outcomes include changes in: OME signs (middle ear fluid) and symptoms (fullness in ear, difficulty in hearing), objective hearing thresholds, episodes of AOM, and vestibular function such as balance and coordination. Treatment options include:

a. Tympanostomy tubes

b. Adenoidectomy with or without myringotomy

c. Myringotomy

d. Oral or topical nasal steroids

e. Autoinflation

f. Complementary and alternative medical procedures

g. Watchful waiting

h. Variations in surgical technique or procedure

KQ 2: What is the comparative effectiveness of the different treatment options listed in KQ 1 (active treatments and watchful waiting) in improving functional and health-related quality-of-life outcomes in patients with OME? Outcomes include: hearing, speech and language development, auditory processing, academic achievement, attention and behavioral outcomes, health-related quality of life, and patient and parent satisfaction with care.

KQ 3: What are the differences in harms or tolerability among the different treatment options?

KQ 4: What are the comparative benefits and harms of treatment options in subgroups of patients with OME? Subgroups include:

a. Patients of different age groups

b. Patients of different racial/ethnic backgrounds

c. Patients in different socioeconomic status groups

d. Patients with comorbidities such as craniofacial abnormalities (e.g., cleft palate), Down syndrome, and existing speech, language, and hearing problems

e. Patients with a medical history of AOM or OME (with and without clinical hearing loss)

KQ 5: Is the comparative effectiveness of treatment options affected by the following: health insurance coverage, physician specialty, type of facility of the treatment provider, geographic location, continuity of care, or prior inoculation with the pneumococcal vaccine?

PICOTS Framework

The PICOTS (Population, Intervention, Comparator, Outcomes, Timing, and Setting) framework does not differ by KQ and is the following:

P:	All individuals with OME. This includes younger and older children, adolescents, adults; individuals from different racial/ethnic backgrounds; and special populations of any age including individuals with craniofacial abnormalities (e.g., cleft palate), Down syndrome, existing hearing loss, delays in speech and language, or a history of acute otitis media (AOM) or OME.
I:	Surgical interventions: tympanostomy tubes (also referred to as pressure equalization [PE] tubes), myringotomy and adenoidectomy with or without myringotomy. Pharmacological treatments: oral or topical nasal steroids. Nonpharmacological and nonsurgical treatments or treatment strategies: watchful waiting, CAM procedures, and autoinflation of the Eustachian tube.
C:	Different combinations of the above interventions and strategies, including: head-to-head comparisons of one or more treatments, treatment strategies (e.g., watchful waiting vs. early treatment), or surgical procedures and techniques (e.g., one type of tympanostomy tube or procedure vs. another). Placebo or no treatment will also be considered as appropriate comparators for oral or nasal steroids only. In the absence of head-to-head trial evidence, we will consider observational data.
O:	Clinical outcomes: changes in middle ear fluid, episodes of AOM, hearing thresholds, vestibular function (i.e., balance and coordination). Health care utilization: number of office visits, number of surgeries, and medication use. Functional and quality-of-life outcomes: hearing, auditory processing, speech and language

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	development, academic achievement, attention and behavior, quality of life, and parental satisfaction with care. Harms: all reported harms for each treatment option will be included.
T:	Short-term studies looking at outcomes from 0–3 months postintervention. Longer term studies looking at outcomes past 3 months and into adolescence or adulthood.
S:	Primary care offices where the patient is seen by a pediatrician, family physician, or nurse practitioner; subspecialist physician offices where the patient is seen by an otolaryngologist; surgical settings within a hospital or outpatient clinic; emergency departments; and craniofacial treatment centers.

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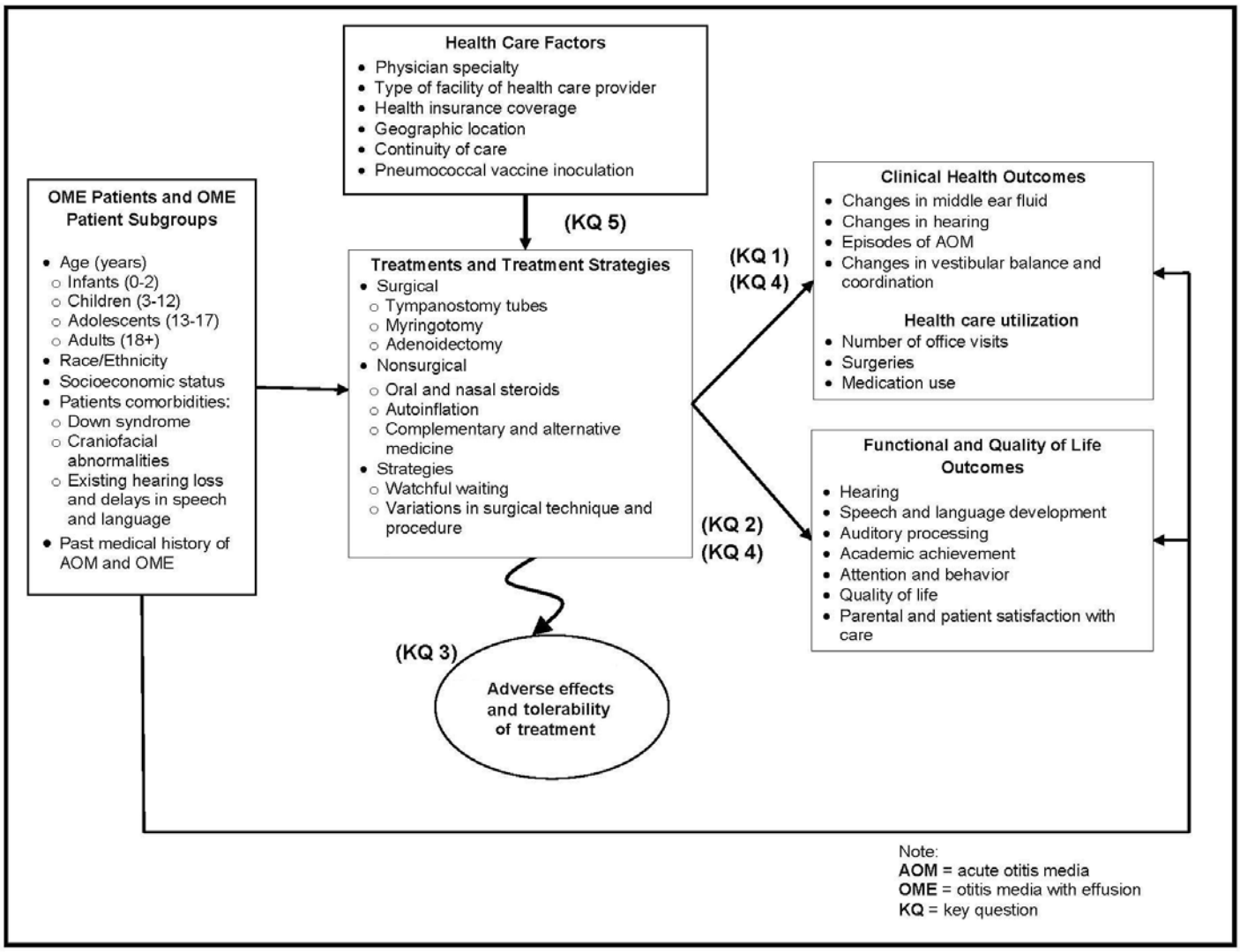
III. Analytic Framework



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review - Studies will be included or excluded in the review based on the PICOTS model outlined in Section II, findings from the topic refinement phase as described in section 1, and the study-specific inclusion criteria listed below in Table 2.

Table 2. Study Inclusion Criteria

Category	Criteria for Inclusion
Study design	Meta-analyses, systematic reviews, RCTs, and nonrandomized controlled trials will be included for each treatment option. Prospective and retrospective cohort studies and case-control studies will be included for KQs that cannot be answered using trial data alone due to gaps in the evidence.
Study duration	Unlimited
By ear or by subject studies	We will include both by ear and by subject studies but will differentiate these two approaches when presenting results.
Time of publication	As described in section 1, some of the treatment options of interest have been comprehensively addressed in recent Cochrane Collaboration or national government-commissioned systematic reviews. For this reason and because of the large volume of literature on the topic, we will search only for new literature when a treatment has been adequately addressed in a review from one of these two types of sources. Each of the earlier reviews that meet this inclusion criterion are listed below. We will include all studies identified by the relevant systematic reviews and will synthesize the existing and new literature as one. An exception to this criterion will be cases in which our TEP finds the existing evidence compelling and the new evidence is unlikely to change earlier findings or likely to have a have a high risk of bias. In these cases, we will simply comment on how the new literature adds to existing conclusions. We will search from 1948 forward for all treatments not addressed in one of the systematic reviews presented below. The following summarizes our search strategy for each included treatment option and population of interest: The literature comprising nonrandomized and observational studies will be searched from 1948 forward across treatment options. **Tympanostomy tubes** *Otherwise healthy children:* Include RCT studies from the two recent systematic reviews relevant to our KQs[13, 15] and search all new RCT literature published since April 2006 forward. *Adults:* Search all literature from 1948 forward. *Special populations as outlined in our PICOTS*: Include RCTs from the two recent systematic reviews relevant to our KQs[13, 15] and search all new

Category	Criteria for Inclusion
	RCT literature published since April 2006 forward. **Adenoidectomy with or without myringotomy** *Otherwise healthy children:* Include RCTs from the recent systematic review relevant to our KQs[16] and search all new RCT literature published since March 2008 forward. *Adults:* Search all literature from 1948 forward. *Special populations as outlined in our PICOTS:* Include RCTs from the recent systematic review relevant to our KQs[16] and search all new RCT literature published since March 2008 forward. **Oral and topical nasal steroids** *Otherwise healthy children:* Include RCTs from the recent systematic review relevant to our KQs[18] and search all new RCT literature published since May 2005 forward. *Adults:* Search all literature from 1948 forward. *Special populations as outlined in our PICOTS:* Include RCTs from the recent systematic review relevant to our KQs[18] and search all new RCT literature published since May 2005 forward. **Autoinflation** *Otherwise healthy children:* Include RCTs from the recent systematic review relevant to our KQs[17] and search all new RCT

Category	Criteria for Inclusion
	literature published since August 2005 forward. *Adults:* Include RCTs from the recent systematic review relevant to our KQs[17] and search all new RCT literature published since August 2005 forward. *Special populations as outlined in our PICOTS:* Include RCTs from the recent systematic review relevant to our KQs[17] and search all new RCT literature published since August 2005 forward. **Complementary and alternative medical procedures** *Otherwise healthy children:* Search all literature from 1948 forward and only include all RCTs. *Adults:* Search all literature from 1948 forward and only include all RCTs. *Special populations as outlined in our PICOTS:* Search all literature from 1948 forward and only include all RCTs. **Myringotomy** *Otherwise healthy children:* Search all literature from 1948 forward. *Adults:* Search all literature from 1948 forward. *Special populations as outlined in our PICOTS:*

Category	Criteria for Inclusion
	Search all literature from 1948 forward. **Watchful waiting** *Otherwise healthy children:* Search all literature from 1948 forward. *Adults:* Search all literature from 1948 forward. *Special populations as outlined in our PICOTS:* Search all literature from 1948 forward. **Variations in surgical technique or procedure** *Otherwise healthy children:* Include RCTs from the recent systematic reviews relevant to our KQs[13] and search all new RCT literature published since April 2006 forward. *Adults:* Include RCTs from the recent systematic reviews relevant to our KQs[13] and search all new RCT literature published since April 2006 forward. *Special populations as outlined in our PICOTS:* Include RCTs from the recent systematic reviews relevant to our KQs[13] and search all new RCT literature published since April 2006 forward.
Language of publication	Given the volume of literature on this topic, we will limit our search to publications in the English language.

*Search to be updated when report is out for peer review.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions - We will systematically search, review, and analyze the scientific evidence for each KQ. To identify articles for this review, we will conduct focused searches of PubMed®, EMBASE®, the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and the Cochrane Library. An experienced research librarian will use a predefined list of search terms and medical subject headings (MeSH®) when applicable. We will limit the search to studies published in English because of limited resources; this may bias the report to include more studies from English-speaking countries.

As described in Table 2 above, we plan to vary the earliest publication date that we will search for RCT evidence based on the existence of studies having been previously identified in recent Cochrane Collaboration or national government-commissioned systematic reviews. We will, therefore, run multiple searches to obtain the most focused meaningful evidence.

We will complete targeted searches for unpublished or grey literature relevant to the review. Methods for identifying grey literature will include a review of trial registries, specifically, ClinicalTrials.gov, Health Services Research Projects in Progress (http://www.nlm.nih.gov/hsrproj/), and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/). Further, AHRQ will also request Scientific Information Packets from the developers or distributors of the interventions identified in the literature review. Scientific Information Packets allow an opportunity for the intervention developers and distributors to provide the Evidence-based Practice Center (EPC) with both published and unpublished data that they believe should be considered for the review. The EPC will review the information provided in the Scientific Information Packets and grey literature. We will include studies that meet all inclusion criteria and contain enough information on research methods to be able to assess the study's risk of bias.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by peer reviewers or public comment respondents will be investigated and, if appropriate, incorporated into the final review. Reference lists of systematic reviews that are pertinent but do not meet our inclusion criteria will be scanned for studies that should be considered for this review. Appropriateness will be determined by the same inclusion and exclusion criteria described in the previous section.

C. **Data Abstraction and Data Management** - All titles and abstracts identified through searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then

make the determination. All results will be tracked in an EndNote® (Thomson Reuters, New York, NY) database.

We will retrieve and review the full text of all articles included during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the research team for inclusion or exclusion on the basis of the eligibility criteria described earlier. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. All results will be tracked in an EndNote database. We will record the reason why each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet the inclusion criteria, we will abstract relevant information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team.

D. Assessment of Methodological Quality of Individual Studies - To assess the risk of bias of studies, we will use the guidance described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[27] We will assess the potential for selection bias, performance bias, attrition bias, detection bias, and reporting bias. Results of this assessment will be summarized in a rating of low, medium, or high risk of bias. In general, a study with a low risk of bias has a strong design (more typically an RCT), measures outcomes appropriately, uses appropriate statistical and analytical methods, reports low attrition, and reports methods and outcomes clearly and precisely. Studies with a medium risk of bias are those that do not meet all criteria required for low risk of bias but do not have flaws that are likely to cause major bias. Missing information often leads to ratings of medium risk as opposed to low risk. Studies with a high risk of bias are those with at least one major flaw that is likely to cause significant bias and thus might invalidate the results and includes errors in study conduct or analysis of results. Studies with a high risk of bias will not be considered in this review. The questions included in the tools we will use to evaluate risk of bias will differ to some extent by study type (e.g., RCT, nonrandomized trial, observational study) to examine the most critical potential sources of bias that are likely to affect that design within the context of this body of literature. Questions concerning the risk of bias of RCTs will be developed from the Cochrane Collaboration's tool for assessing risk of bias,[28] and questions concerning the risk of bias of nonrandomized and observational studies will be developed from the RTI Item Bank on Risk of Bias and Precision of Observational Studies.[27]

Two independent reviewers will assess the risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

E. Data Synthesis - If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. To determine whether quantitative analyses are appropriate, we will assess the clinical heterogeneity using the PICOTS framework and following established guidance.[29] We will consider similarities and differences by PICOTS, sociodemographic factors (e.g., race, ethnicity, age, socioeconomic status), and study design. If quantitative analysis is appropriate, we will evaluate the statistical heterogeneity of pooled analysis using the chi-squared statistic and the I^2 statistic (the proportion of variation in the study estimates due to heterogeneity).

When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in reporting), we will synthesize the data qualitatively.

F. Equivalence-Noninferiority - We will consider the potential equivalence (whether a new treatment is therapeutically similar to a standard treatment within a predefined margin of equivalence) and noninferiority—a newer treatment thought to be superior to an older treatment on certain outcomes unrelated to effectiveness (e.g., fewer side effects, lower cost, and/or greater convenience) is not less effective than the older treatment by some prespecified margin of acceptability. Whether we can make these equivalence-noninferiority comparisons will depend on whether a minimum important difference can be justified for particular outcomes. We will make that determination early in the review process, before the evaluation of the included literature with input from our TEP.

G. Grading the Evidence for Each Key Question - We will grade the overall strength of the body of evidence on the basis of guidance established for the EPC Program.30 This approach incorporates four key domains: risk of bias (including study design and aggregate risk of bias across studies), consistency, directness, and precision of the evidence. The grades of evidence that can be assigned are described in Table 3. Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions in this review. Two reviewers will assess each domain and the overall grade for each key outcome listed in the PICOTS framework, and conflicts will be resolved by consensus.

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate	Moderate confidence that the evidence reflects the true effect: Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect: Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010[30]

H. Assessing Applicability - We will assess the applicability both of individual studies and of the body of evidence. For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Such conditions may be associated with heterogeneity of treatment effect and the ability to generalize the effectiveness of an intervention to use in everyday practice.

To assess the applicability of a body of evidence, we will consider the consistency of results across studies that represent an array of different populations or a specific subpopulation of interest (e.g. individuals with comorbidities such as craniofacial abnormalities or Down syndrome).

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VI. Definition of Terms

Source: www.effectivehealthcare.ahrq.gov
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Acute otitis media: An acute infection of the middle ear that can be viral and/or bacterial in origin.

Audiometry: The testing of hearing ability that includes determination of the hearing levels, ability to discriminate between various sound intensities, ability to distinguish speech from background noise and other aspects. Pure tone audiometry and impedance audiometry (tympanometry) are two of the commonly used tests for audiometric evaluation.

Autoinflation: A technique whereby the Eustachian tube (the tube that connects the middle ear and the back of the nose) is reopened by raising pressure in the nose. This can be achieved by forced exhalation with closed mouth and nose, blowing up a balloon through each nostril or using an anesthetic mask. The aim is to introduce air into the middle ear, via the Eustachian tube, equalizing the pressures and allowing better drainage of the fluid.

Myringotomy: A surgical procedure in which an incision is made in the tympanic membrane. It may be performed as a single procedure or as a preparation for insertion of a tympanostomy tube.

Otitis media with effusion: A collection of fluid in the middle ear without signs or symptoms of ear infection.

Otoscopy: The clinical examination of the ear canal and tympanic membrane, usually by means of a hand-held auriscope (also known as an otoscope) providing illumination and magnification. Sometimes an attachment is used that permits insufflation of air into the ear canal so that the mobility of the tympanic membrane can be assessed, and this is known as pneumatic otoscopy.

Tympanogram: A curve showing the transmission of energy through the middle ear at various air pressures in the external auditory canal. It gives a crude but objective assessment of conductive hearing loss, and various middle ear disorders yield distinctive patterns of tympanogram:

- **Tympanogram A:** a symmetrical triangular graph with its peak at zero pressure level represents normal middle ear function.
- **Tympanogram B:** a flat line on the graph represents the middle ear space filled with fluid, restricting movement of the tympanic membrane under the externally applied pressure.
- **Tympanogram C:** this pattern is found when there is a reduction of middle ear pressure relative to the air pressure in the external auditory canal, which causes inward retraction of the tympanic membrane; the graph shows the shift of the tympanographic peak into the negative value range, but it is of a normal shape.

Tympanometry: Also known as impedance audiometry, the test measures how readily the middle ear system (the tympanic membrane and the middle ear ossicles) can be set into vibration with a change of air pressure in the external auditory canal. In the normal ear, maximum sound transmission occurs when the

air pressure within the middle ear space is the same as the atmospheric pressure, that is, equal to the air pressure in the external auditory canal.

Watchful waiting: Watchful waiting or active observation, as it has more recently been called, is the process of regular review and followup of the child, including assessments of hearing, development, and educational progress.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
7/30/2012	II	In the Picots table; in the comparator description box: "Different combinations of the above interventions and strategies, including: head to-head comparisons of one or more treatments, treatment strategies (e.g., watchful waiting vs. early treatment), or surgical procedures and techniques (e.g., one type of tympanostomy tube or procedure vs. another). In the absence of head-to head trial evidence, we will consider observational data."	In the Picots table; in the comparator description box: "Different combinations of the above interventions and strategies, including: head-to head comparisons of one or more treatments, treatment strategies (e.g., watchful waiting vs. early treatment), or surgical procedures and techniques (e.g., one type of tympanostomy tube or procedure vs. another). Placebo or no treatment will also be considered as appropriate comparators for oral or nasal steroids only. In the absence of head-to-head trial evidence, we will consider observational data." "Placebo or no treatment will also be considered as appropriate comparators for oral	To provide clarification.

			or nasal steroids only" added to comparator description in Picots table.	
7/30/2012	III	In the analytic framework, in the Treatment and Treatment strategies box, antimicrobials is listed.	Antimicrobials were removed from the analytic framework.	Antimicrobials which include antibiotics are currently are not commonly used in the United States to treat OME and are not recommended in current U.S. guidelines. However, there is some conflicting evidence regarding antibiotics for the treatment of OME and an upcoming Cochrane Collaboration review on the use of antibiotics for the treatment of OME in children was started in 2011 and is well underway. We will not duplicate their efforts and have excluded antibiotics from the current comparative review. (per protocol submitted 2/13/12)
7/30/2012	III	In the analytic framework,	Adherence is removed	Not pertinent to

		adherence is listed in the KQ3 representation,.	from the analytic framework.	this Key Question.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

None.

XIII. Role of the Funder

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