

## Evidence-based Practice Center Systematic Review Protocol

Project Title: Tonsillectomy for Obstructive Sleep-Disordered Breathing or Recurrent Throat Infection  
in Children

Initial publication date if applicable: November 9, 2015

Amendment Date(s) if applicable: December 3, 2015, February 10, 2016

(Amendments Details—see Section VII)

### I. Background and Objectives for the Systematic Review

Tonsillectomy or adenotonsillectomy is commonly performed in the U.S. The entities together represent more than 15% of all surgical procedures in children under the age of 15 years.<sup>1</sup> Traditionally, tonsillectomy or adenotonsillectomy were performed for recurrent throat infections; however, recently more procedures are being performed for obstructive sleep-disordered breathing (OSDB) and obstructive sleep apnea.<sup>2,3</sup> Historically, tonsillectomy rates have varied widely. In their seminal study, Wennberg and Gittlesohn found the rate of tonsillectomy varied almost 12-fold across adjacent counties in rural Vermont with similar populations.<sup>4</sup> Variation in rates continues despite improved evidence about indications.<sup>5</sup>

Table 1 outlines surgical techniques commonly used for tonsillectomy or adenotonsillectomy. Choice of technique may depend on factors including the underlying indication for surgery (e.g., recurrent throat infection). Each approach has proponents, with each group advocating that its approach causes less pain and reduces risk of postoperative bleeding. All procedures are performed under general anesthesia.

Hereafter, we use the term tonsillectomy to refer to removal of the tonsils alone, removal of tonsils and adenoids (adenotonsillectomy), and partial removal of the tonsils (tonsillotomy) using any surgical technique or approach.

**Table 1. Commonly used surgical techniques or tools for tonsillectomy**

Surgical Technique or Tool	Description
Cold dissection	Tonsils dissected and removed from oropharynx (tonsillar fossae) using a scalpel or other means that do not include cautery.
Electrocautery	Tonsils dissected and removed from oropharynx (tonsillar fossae) using electrocautery (e.g., heated needle or spatula).
Harmonic scalpel	Tonsils dissected and removed from oropharynx using ultrasonically energized scalpel.
Microdebridement	Tonsils removed from oropharynx (tonsillar fossae) using a microdebrider which suctions tonsillar tissue into a rotary blade that morcellates and removes tissue. All or part of the tonsil is removed with this technique.
Laser ablation	Tonsils removed with a handheld laser wand that allows dissection and removal of the tonsil from the oropharynx (tonsillar fossae). Carbon dioxide laser is most common used type.
Coblation	Tonsils dissected and removed from oropharynx using low-temperature irrigation radio frequency energy device.

Indications for tonsillectomy for recurrent infection have been defined as “severe tonsillitis.” Severe tonsillitis has itself been defined as (1) five or more episodes of true tonsillitis a year; (2) symptoms for at least a year; and (3) episodes that are disabling and prevent normal functioning.<sup>6</sup> No gold standard methods exist to diagnose an episode of tonsillitis or to attribute symptoms to tonsillitis predictably; neither does any consensus exist on what symptoms attributable to tonsillitis are disabling. Usually, bacterial pharyngitis is confirmed via rapid testing or culture, but whether the tonsils are the harboring infection source cannot be definitely proven.

Many practitioners treat sore throat empirically with antibiotics without objective testing.<sup>7</sup> Thus, many cases termed “tonsillitis” may be unrelated to the tonsils.<sup>8</sup> Infections will also vary in the level of documentation in the child’s medical record, which makes comparing severity and numbers of infections challenging.<sup>9-11</sup>

Tonsillectomy may also be performed in cases of OSDB (defined here as breathing difficulties during sleep as operationalized in each study in the review, including obstructive sleep apnea and upper airway resistance syndrome). Recognition has been growing that adenotonsillar hypertrophy can be a factor in OSDB in children. OSDB includes disorders ranging from snoring to obstructive sleep apnea (OSA). The consequences of these sleep-related disorders include an attributable average intelligence quotient loss of five points, hypersomnolence, emotional lability, decreased attention, small stature, enuresis, cardiopulmonary morbidity, and missed school. Treatment of OSDB may improve behavior, attention, quality of life, neurocognitive functioning, enuresis, parasomnias, and restless sleep, and it may also reverse cardiovascular sequelae of OSA.<sup>12, 13</sup> Further, children with certain developmental disorders and craniofacial syndromes, including Down Syndrome, have particularly high rates of OSDB and baseline comorbidities that OSDB may exacerbate; they represent a vulnerable population for which good data are needed.

As in adults, OSA in children is diagnosed via polysomnography, and treatment may involve approaches to eliminate potential contributing factors. One OSA treatment is continuous positive airway pressure (CPAP), which is a device that children wear over their faces. The CPAP device provides continuous high pressure that holds the upper airway open as children sleep. Children’s compliance with CPAP is variable.<sup>14-18</sup> Other approaches advocated in certain circumstances include weight loss in overweight children, orthodontic devices to expand the oral palate, or allergy or other medications to treat breathing symptoms. However, often the site of obstruction of air during sleep is in the oropharynx, which in children is crowded because of tonsillar hypertrophy. Removal of the tonsils opens up the airway and has the potential to create enough space in the oropharynx that the child no longer has obstructive events at night.

Regardless of indication, age may affect outcomes markedly in tonsillectomy; younger children tend to respond favorably and older children not as well.<sup>19, 20</sup> Younger children, however, also typically have greater operative risks. The demarcation between younger and older ages is not well defined. Obesity may also differ by age range, which may in turn affect the incidence of OSDB in different age ranges.

Oropharyngeal surgery may present children with difficulty returning to normal diets, maintaining adequate hydration, edema that could result in airway obstruction, and postoperative nausea and vomiting. To help minimize these concerns, tonsillectomy may also involve perioperative use of antibiotics, steroids, and pain medications. A 2012 Cochrane review examining the effect of perioperative systemic antibiotics on post-tonsillectomy morbidity (pain, consumption of pain medications, secondary hemorrhage, fever, and return to normal diet) failed to find any clinically important impact of antibiotics in reducing pain, need for analgesia, or secondary hemorrhage.<sup>21</sup> However, this analysis combined adult and pediatric trials; thus, the applicability to children alone is not clear. Furthermore, this study included only randomized controlled trials (RCTs). The role of perioperative anti-inflammatory medications (e.g., non-steroidal anti-inflammatory drugs [NSAID]) and systemic steroids is contentious. Postoperative medications may reduce nausea and vomiting, postoperative swelling, and operative site pain, but many clinicians are concerned about potential increased risk of postoperative hemorrhage, which can lead to readmission and re-operation.<sup>22</sup> Findings have been inconsistent and data are heterogeneous even among prior systematic reviews of the effectiveness and harms of antibiotics, steroids, and NSAIDs in the perioperative period in children undergoing tonsillectomy.

The objective of the current review is to address the comparative effectiveness and harms of

tonsillectomy in children with the most common indications for the procedure, namely, OSDB and recurrent throat infections. Prior systematic reviews have typically included studies with both children and adults, or have addressed specific facets of treatment, or have included only RCT data. The current review, nominated by the American Academy of Otolaryngology Head and Neck Surgery Foundation, will address key decisional dilemmas identified by stakeholders and through our preliminary scan of the literature in a comprehensive manner. Specifically, we will include both RCTs and prospective observational studies with comparison groups. The review will also specify analyses to improve understanding of outcomes in subgroups such as very young children (1-2 years old) and children who are overweight or obese. Given the heterogeneity of approaches to tonsillectomy and covariates associated with underlying indications, we will stratify presentation and analysis of results for all Key Questions by key factors (e.g., BMI, level of documentation of throat infections, streptococcal infections, specific surgical tool such as microdebrider) where possible. A comprehensive review will inform the development of guidelines that may reduce practice variation and assist clinicians and caregivers with treatment choices.

## II. The Key Questions

The six Key Questions (KQ) specified below evolved from the EPC team discussions, expert input, and comments received during public posting of the draft KQ to the AHRQ Effective Health Care web site from July 23, 2015, to August 10, 2015. Four individuals made comments. Commenters generally concluded that the KQs were comprehensive and addressed important clinical decision points. Some comments suggested that we needed to clarify comparator medications or specify additional outcomes of interest, such as including peritonsillar abscess and neck infection as complications of recurrent throat infections. We revised the KQs and population, intervention, comparator, outcome, timing, and setting (PICOTS) characteristics accordingly. Other comments suggested presenting results by subgroup when possible (e.g., indication for tonsillectomy), and, as noted, the review will attempt to do so whenever feasible.

Some comments also discussed intermediate outcomes such as intraoperative blood loss. As the review is focused on ultimate health outcomes of interest to children and caregivers, we elected not to address these intermediate outcomes. Some comments advocated addressing the cost-effectiveness of tonsillectomy techniques; however, this type of analysis is beyond the scope of the current review.

The final six KQs and subquestions are listed below. We note that OSDB includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome. Tonsillectomy includes tonsillectomy, partial tonsillectomy, and adenotonsillectomy. We also note that comparative effectiveness includes both the benefits and harms of interventions.

1. In children with obstructive sleep-disordered breathing (OSDB), what is the comparative effectiveness of tonsillectomy compared with continuous positive airway pressure (CPAP), or watchful waiting with supportive care (including pharmacologic treatment) to improve sleep outcomes, cognitive or behavioral outcomes, and health outcomes?
  - 1a. In children with OSDB and neuromuscular or craniofacial abnormalities, what is the comparative effectiveness of tonsillectomy compared with CPAP, or watchful waiting with supportive care (including pharmacologic treatment) to improve sleep outcomes, cognitive or behavioral outcomes, and health outcomes?
  - 1b. In children with OSDB under age 3 years, what is the comparative effectiveness of tonsillectomy compared with watchful waiting with supportive care (including pharmacologic treatment) to improve sleep outcomes, cognitive or behavioral outcomes, and health outcomes?

1c. In children with OSDB and Down syndrome, what is the comparative effectiveness of tonsillectomy compared with CPAP, or watchful waiting with supportive care (including pharmacologic treatment) to improve sleep outcomes, cognitive or behavioral outcomes, and health outcomes?

1d. In children with OSDB who are overweight or obese, what is the comparative effectiveness of tonsillectomy compared with CPAP, weight loss, or watchful waiting with supportive care (including pharmacologic treatment) to improve sleep outcomes, cognitive or behavioral outcomes, and health outcomes?

2. Among children with recurrent throat infections, what is the comparative effectiveness, including harms, of tonsillectomy compared with watchful waiting with supportive care (including pharmacologic--antibiotic or non-antibiotic--treatments) on the number and severity of throat infections, quality of life, and health care utilization?
3. Do benefits and harms differ between partial tonsillectomy and total tonsillectomy?
4. Do benefits and harms differ by surgical technique (e.g., cautery, coblation)?
5. What are the benefits and harms of adjunctive perioperative (i.e., preoperative, intraoperative, or in post-anesthesia care) pharmacologic agents intended to improve outcomes?
6. What are the benefits and harms of postoperative (i.e., after discharge from post-anesthesia care and up to 10 days post-surgery) pharmacologic agents intended to reduce pain-related outcomes?

Table 2 outlines PICOTS characteristics for each KQ.

Table 2. Population, intervention, comparator, outcome characteristics\*

KQ	Population	Intervention <sup>†</sup>	Comparators	Outcomes
1	Children (3-18 years of age) with OSDB**	Tonsillectomy	-Continuous positive airway pressure (CPAP) -Pharmacologic treatment including anti-inflammatory medications, decongestants, allergy medication, antihistamines, nasal steroids, leukotriene inhibitors	<p>Sleep outcomes</p> <ul style="list-style-type: none"> <li>-Apnea Hypopnea Index (AHI)</li> <li>-Sleep quality measures (Obstructive Sleep Apnea-18 [OSA-18], Clinical Assessment Score-15 [CAS-15])</li> <li>-Pediatric Sleep Questionnaire (PSQ)</li> <li>-Modified Epworth Sleepiness Scale</li> <li>-Desaturation nadir</li> <li>-OSDB persistence</li> </ul> <p>Cognitive or behavioral outcomes</p> <ul style="list-style-type: none"> <li>-Validated measures of attention, irritability, and memory</li> </ul> <p>Health outcomes</p> <ul style="list-style-type: none"> <li>-Growth velocity (height, BMI for age)</li> <li>-Cardiopulmonary issues</li> <li>-Self or caregiver-reported enuresis</li> <li>-Health care utilization (number of clinician visits)</li> </ul> <p>Harms</p> <ul style="list-style-type: none"> <li>-Re-admission or ER visit or ICU admission for postoperative pain, dehydration, bleeding, or nausea and vomiting</li> <li>-Reoperation for primary or secondary bleeding</li> <li>-Velopharyngeal insufficiency</li> <li>-30-day mortality</li> <li>-Harms of comparator agents reported in studies with comparison groups</li> </ul>
1a	Children (3-18 years of age) with OSDB and neuromuscular or craniofacial abnormalities	Tonsillectomy	See comparators above (KQ1)	See outcomes above (KQ1)
1b	Children under age 3 with OSDB	Tonsillectomy	See comparators above (KQ1)	See outcomes above (KQ1) Length of stay
1c	Children (3-18 years of age) with OSDB and Down syndrome	Tonsillectomy	See comparators above (KQ1)	See outcomes above (KQ1) Length of stay
1d	Children (3-18 years of age) with OSDB who are overweight or obese	Tonsillectomy	-CPAP -Weight loss -Pharmacologic treatment including anti-inflammatory medications, decongestants, allergy	See outcomes above (KQ1)

KQ	Population	Intervention <sup>†</sup>	Comparators	Outcomes
			medication, antihistamines, nasal steroids, leukotriene inhibitors	
2	Children (3-18 years) with recurrent throat infections	Tonsillectomy	-Antibiotics -Nonantibiotic pharmacologic treatments (e.g., anti-inflammatory agents, decongestants, antihistamines, leukotriene inhibitors, nasal or systemic steroids)	<p>Throat infections</p> <ul style="list-style-type: none"> <li>-Number of throat infections/year</li> <li>-Severity of throat infections</li> <li>-Number of streptococcal infections/year</li> </ul> <p>Quality of life</p> <ul style="list-style-type: none"> <li>-Validated quality of life measures</li> <li>-Missed school or work for child or caregiver</li> </ul> <p>Other outcomes</p> <ul style="list-style-type: none"> <li>-Health care utilization (number of clinician visits, number of courses of antibiotics)</li> </ul> <p>Harms</p> <ul style="list-style-type: none"> <li>- ER visit or hospital or ICU admission for postoperative pain, bleeding, dehydration, or nausea and vomiting</li> <li>-Reoperation for primary or secondary bleeding</li> <li>-Velopharyngeal insufficiency</li> <li>-30-day mortality</li> <li>-Harms of comparator agents reported in studies with comparison groups</li> </ul>
3	Children (3-18 years) undergoing tonsillectomy	Total tonsillectomy	-Partial tonsillectomy	<p>See sleep, cognitive or behavioral, and health outcomes (KQ1) and quality of life outcomes (KQ2)</p> <p>Throat infections</p> <ul style="list-style-type: none"> <li>-Number of throat infections/year</li> <li>-Severity of throat infections</li> <li>-Number of streptococcal infections/year</li> </ul> <p>Other outcomes</p> <ul style="list-style-type: none"> <li>-Symptomatic tonsillar regrowth</li> <li>-Time to return to usual activity (diet, school)</li> </ul> <p>Harms</p> <ul style="list-style-type: none"> <li>See KQ1</li> <li>Reoperation for complete tonsillectomy</li> </ul>
4	Children (3-18 years) undergoing tonsillectomy	Tonsillectomy	-Other technique for tonsillectomy	<p>See sleep, cognitive or behavioral, and health outcomes (KQ1) and quality of life outcomes (KQ2)</p> <p>Throat infections</p> <ul style="list-style-type: none"> <li>-Number of throat infections/year</li> <li>-Severity of throat infections</li> <li>-Number of streptococcal infections/year</li> </ul>

KQ	Population	Intervention <sup>†</sup>	Comparators	Outcomes
				Other outcomes -Time to return to usual activity (diet, school)  Harms See KQ1
5	Children (3-18 years) undergoing tonsillectomy	Tonsillectomy plus adjunctive perioperative (i.e., preoperative, intraoperative, or immediate postoperative [post-anesthesia care] periods) pharmacologic agents	-Tonsillectomy without adjunctive perioperative pharmacologic agents (i.e., pharmacologic agents given to attempt to reduce postoperative morbidity including pain or nausea and vomiting )	-Pain management -Time to return to usual activities (diet, school) -Health care utilization (number of clinician visits, number of courses of antibiotics)  Harms -Harms of agent -Re-admission to hospital or ICU or ER visit for postoperative pain, bleeding, dehydration, or nausea and vomiting -Reoperation for primary or secondary bleeding -30-day mortality
6	Children (3-18 years) undergoing tonsillectomy and receiving pharmacologic agents for pain postoperatively (i.e., up to 10 days after discharge from post-anesthesia care)	Tonsillectomy plus postoperative pharmacologic agents for pain (e.g., NSAID, ketorolac)	-Tonsillectomy with other postoperative pharmacologic agents for pain	See outcomes and harms for KQ5

Studies of any length or follow-up and in any setting, except for KQ6, which includes pharmacologic agents for pain given up to 10 days post-surgery.

<sup>†</sup>Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

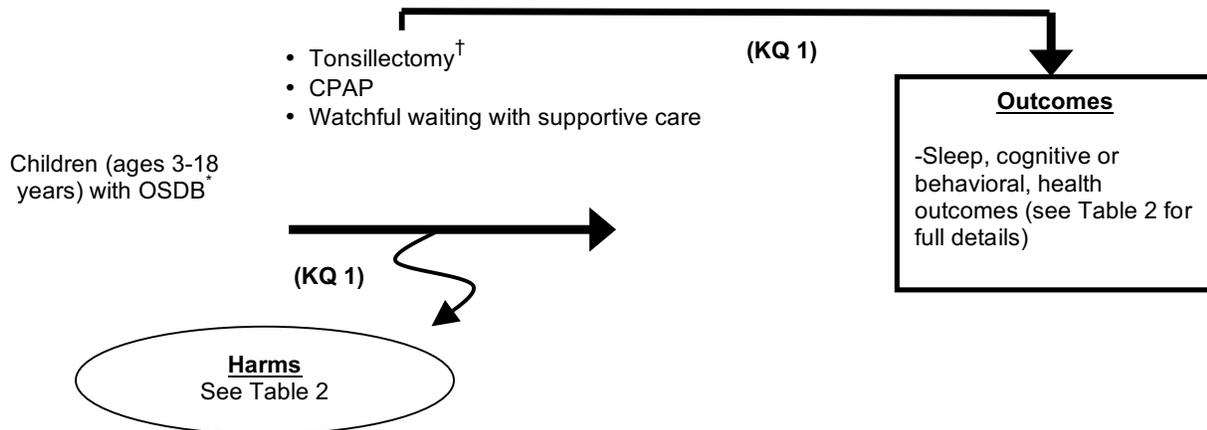
<sup>†</sup>Tonsillectomy includes tonsillectomy, adenotonsillectomy, partial tonsillectomy

Abbreviations: AHI = Apnea Hypopnea Index; BMI = Body Mass Index; CAS-15 = Clinical Assessment Score-15; CPAP = Continuous Positive Airway Pressure; ER = Emergency Room; KQ = Key Question; NSAID = Non-steroidal Anti-Inflammatory Drug; OSA-18 = Obstructive Sleep Apnea-18; OSDB = Obstructive Sleep-Disordered Breathing

### III. Analytic Framework

The following analytic frameworks outline the KQs within the context of the patient, intervention, comparator, and outcomes (PICOS) parameters described for each.

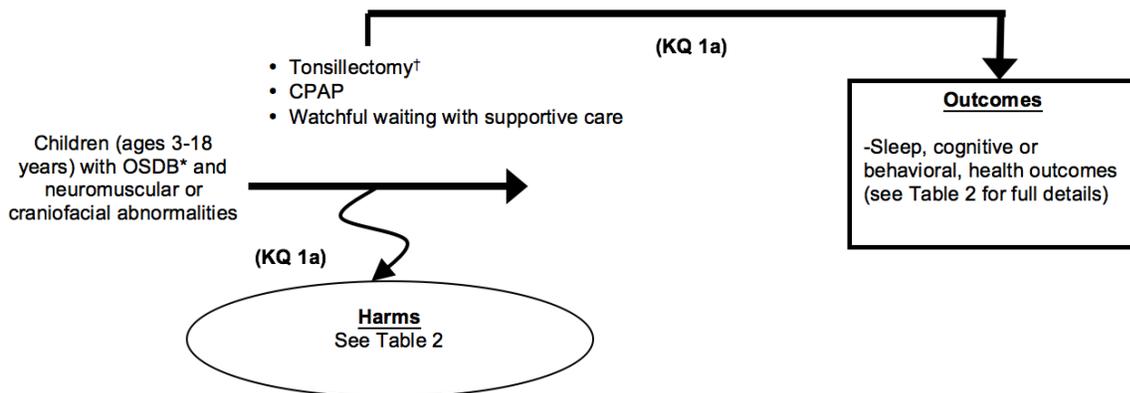
**Figure 1. Analytic framework for Key Question 1**



\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

<sup>†</sup>Includes tonsillectomy, adenotonsillectomy, or partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser) Abbreviations: CPAP = Continuous Positive Airway Pressure; KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

**Figure 2. Analytic framework for Key Question 1a**

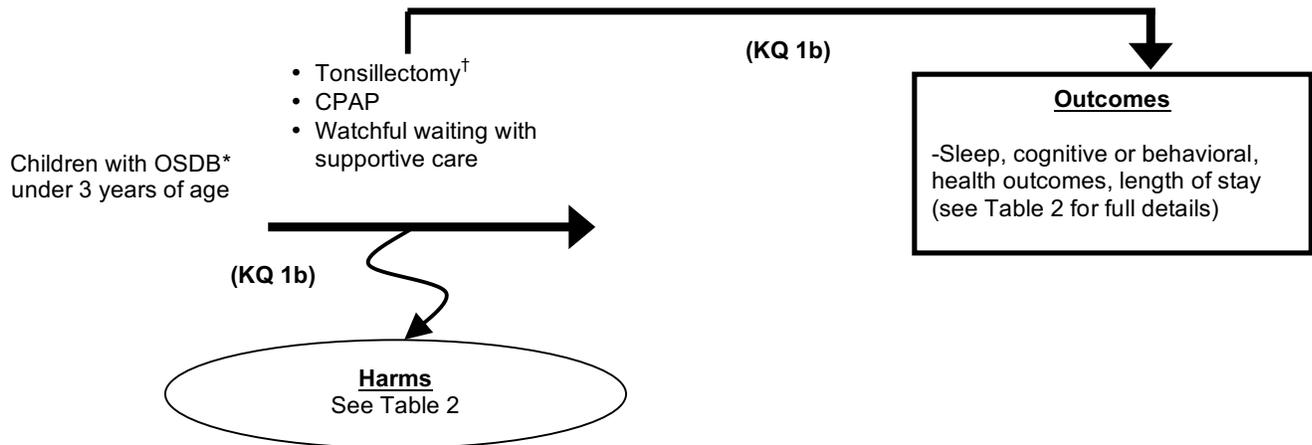


\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

<sup>†</sup>Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser)

Abbreviations: CPAP = Continuous Positive Airway Pressure; KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

**Figure 3. Analytic framework for Key Question 1b**

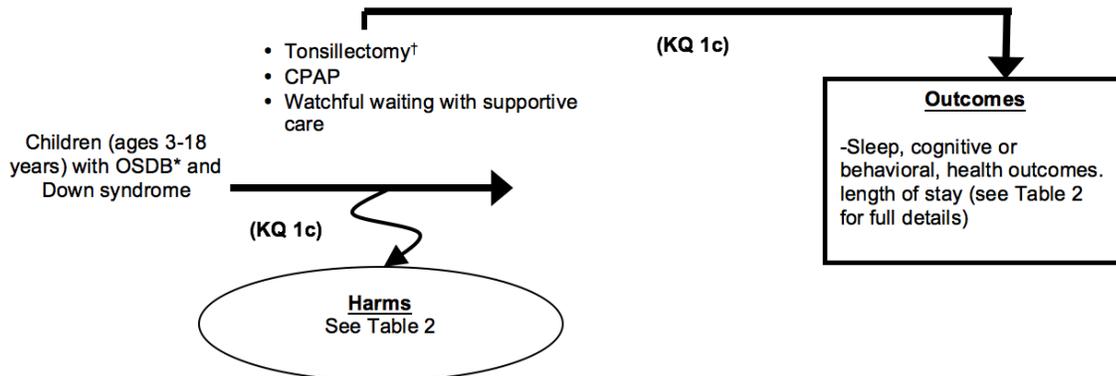


\* Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

† Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser)

Abbreviations: CPAP = Continuous Positive Airway Pressure; KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

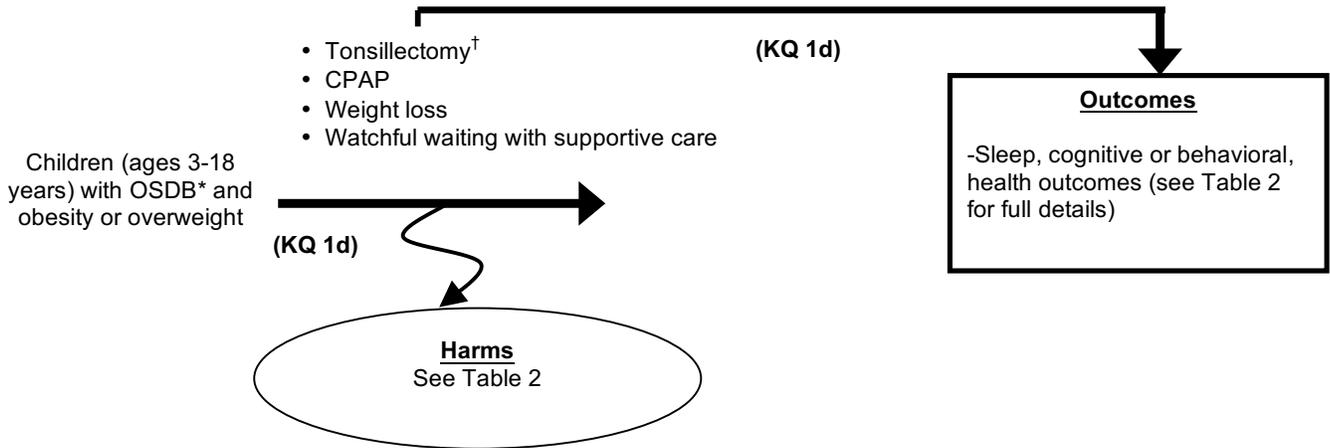
**Figure 4. Analytic framework for Key Question 1c**



\* Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

† Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser) Abbreviations: CPAP = Continuous Positive Airway Pressure; KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

**Figure 5. Analytic framework for Key Question 1d**

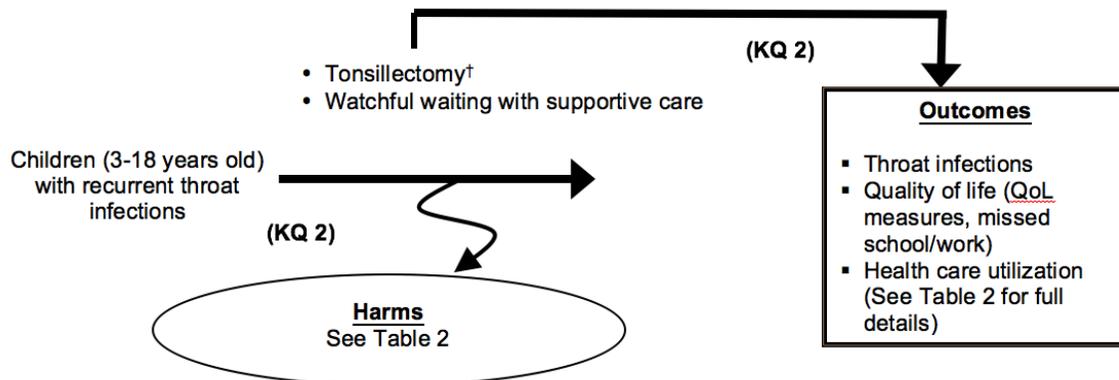


\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

†Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser)

Abbreviations: CPAP = Continuous Positive Airway Pressure; KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

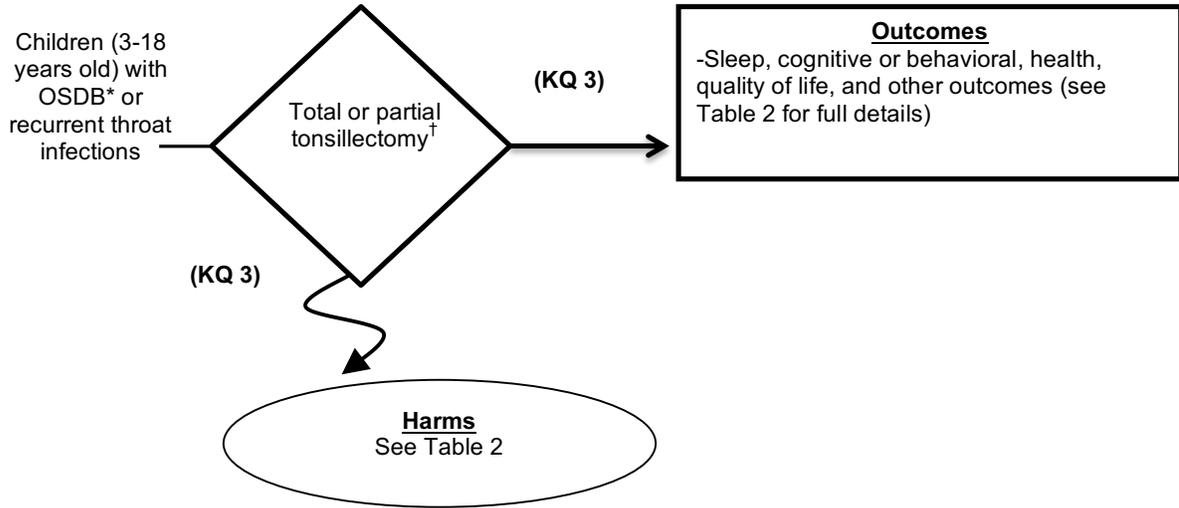
**Figure 6. Analytic framework for Key Question 2**



†Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser)

Abbreviations: KQ = Key Question; QoL = Quality of Life

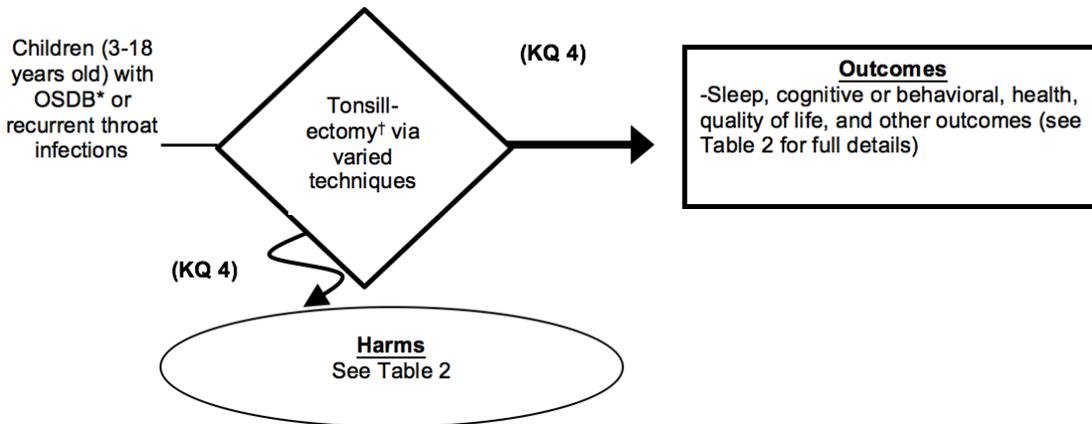
**Figure 7. Analytic framework for KQ3**



\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

†Includes tonsillectomy or adenotonsillectomy. Abbreviations: KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

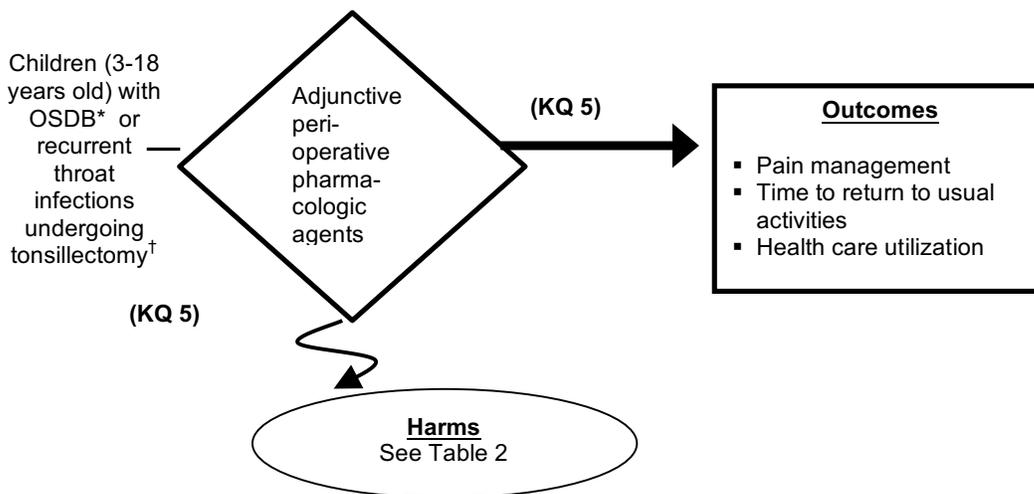
**Figure 8. Analytic framework for KQ4**



\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

†Includes tonsillectomy or adenotonsillectomy. Abbreviations: KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

**Figure 9. Analytic framework for KQ5**

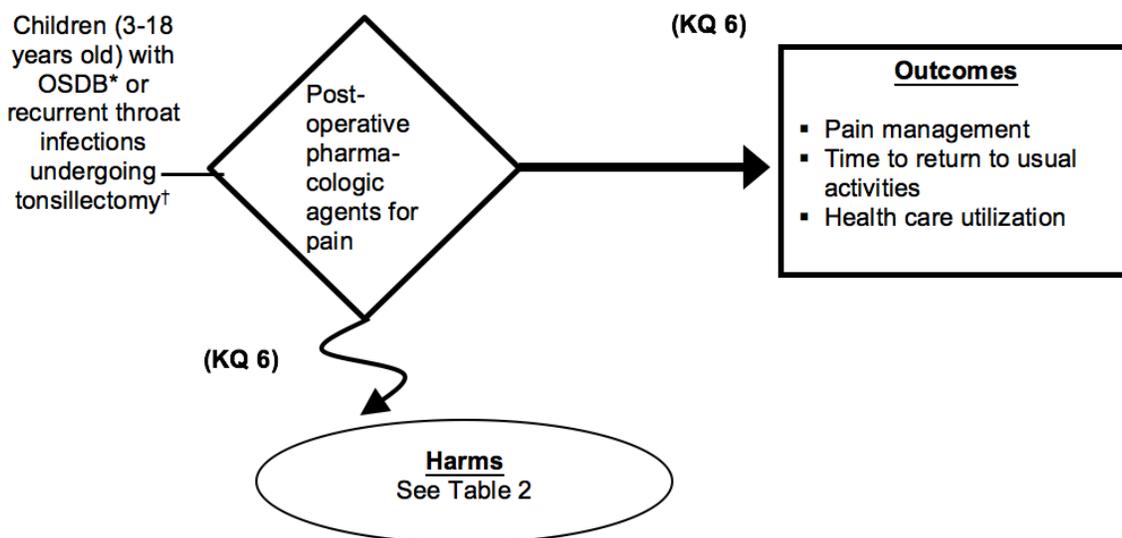


\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

†Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser).

Abbreviations: KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing

**Figure 10. Analytic framework for KQ6**



\*Includes breathing difficulties during sleep as operationalized in each study, including obstructive sleep apnea and upper airway resistance syndrome

†Includes tonsillectomy, adenotonsillectomy, partial tonsillectomy performed using any method or approach (e.g., coblation, cold dissection, laser). Abbreviations: KQ = Key Question; OSDB = Obstructive Sleep-

Disordered Breathing

#### IV. Methods

The methods for this systematic review will follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*<sup>23</sup> and reporting standards in the PRISMA-P checklist.<sup>24</sup> We will register the final protocol in Prospero (<http://www.crd.york.ac.uk/PROSPERO/>).

#### **Criteria for Inclusion of Studies in the Review**

We will use a date limit of January 1, 1980, to the present for the search of indexed literature. In the opinion of our content experts and key informants, the 1980 start date will retrieve seminal earlier studies addressing tonsillectomy but still reflect approaches currently in use.

We will include studies published in English only. We scanned a random sample of 100 non-English abstracts retrieved by our MEDLINE search (25 selected from each decade 1980 to 2015). Most studies appeared to be case series, narrative reviews, imaging or basic science studies, or studies dealing with malignant lesions. Only two studies appeared to meet inclusion criteria; thus, given the high percentage of ineligible items in this scan (98%), we concluded that excluding non-English studies will not introduce significant bias into the review. We will, however, re-assess a sample of non-English studies as we update our MEDLINE search. The team will evaluate any additional non-English studies that appear relevant to determine whether and, if so, how these studies should be addressed in the review (e.g., appendix providing relevant information gleaned from abstract).

Eligible studies for effectiveness outcomes for all KQs must be comparative (studies including an intervention and a comparison group, such as RCTs, prospective cohort studies, nonrandomized trials, case-control studies) studies evaluating the benefits or harms of tonsillectomy (tonsillectomy, adenotonsillectomy, and partial tonsillectomy conducted using any surgical technique such as cautery or cold dissection) compared with an inactive control or alternate intervention. We will also include database or registry studies or case series with at least 1000 participants to address harms of tonsillectomy. We selected the limit of 1000 as we anticipate larger observational studies of harms of tonsillectomy in the literature, and the larger sample size should allow us to capture data on rarer adverse events.

We will report harms of comparator agents or interventions as reported in studies with comparison groups. To ensure that we present a balanced view of potential harms, we will seek recent systematic or comprehensive reviews of harms of agents (e.g., antibiotics, anti-inflammatory agents, allergy medications) used in studies included in the review, which have typically been well-studied, and include a summary in the report or report appendices.

We will use a best evidence approach to determine final inclusion of studies (i.e., If evidence from randomized studies is insufficient to address a KQ or specific outcomes, we will consider evidence from observational literature as well as factors related to the relevance of studies to determine if the inclusion of additional studies is warranted).<sup>25</sup>

Eligible studies must also report one or more outcomes of interest and include children at least 3 years of age and up to and including age 18. Studies addressing KQ1b will include children between 1 and 2 years old. We will require that studies including mixed

age populations (children and adults) either report data separately by age group or include at least 80% children (3-18 years of age).

Children included in studies must be candidates for tonsillectomy because of OSDB (as defined in each study) or recurrent throat infection (KQs 1-6). Subquestions under KQ1 identify specific population parameters (Table 2). We will not require specific operationalization or diagnostic criteria for OSDB or recurrent throat infection; rather, we will capture how each study operationalizes these indications and potentially assess variations in operationalization as modifiers of outcomes.

We summarize the inclusion criteria in Table 3.

**Table 3. Inclusion criteria for studies of tonsillectomy**

Category	Criteria
Population	<ul style="list-style-type: none"> <li>• Children with OSDB age 3-18 years, inclusive (KQ1)</li> <li>• Children with neuromuscular or craniofacial abnormalities and OSDB age 3-18 years, inclusive (KQ1a)</li> <li>• Children under age 3 years with OSDB (KQ1b)</li> <li>• Children with Down syndrome OSDB age 3-18 years, inclusive (KQ1c)</li> <li>• Children with obesity or overweight and OSDB age 3-18 years, inclusive (KQ1d)</li> <li>• Children with recurrent throat infection age 3-18 years, inclusive (KQ2)</li> <li>• Children with OSDB or recurrent throat infection undergoing tonsillectomy age 3-18 years, inclusive (KQ 4-6)</li> </ul>
Design	<ul style="list-style-type: none"> <li>• <b>Effectiveness outcomes:</b> Comparative studies (RCTs, cohort studies with comparison groups, nonrandomized trials, case-control studies) (KQ1-6)</li> <li>• <b>Harms:</b> Comparative studies (RCTs, cohort studies with comparison groups, nonrandomized trials, case-control studies), database or registry studies (harms of tonsillectomy), case series with at least 1000 participants (harms of tonsillectomy)</li> </ul>
Other	<ul style="list-style-type: none"> <li>• Original research (KQ1-6)</li> <li>• Publication language: English (KQ1-6)</li> <li>• Publication year: 1980-present (KQ1-6)</li> <li>• Reports one or more of the outcomes described in Table 2</li> <li>• Sufficiently detailed methods and results to enable data extraction (KQ1-6)</li> <li>• Reports outcome data by target population or intervention (KQ1-KQ6) or if results of mixed age populations reported in aggregate, includes at least 80% children</li> </ul>

Abbreviations: KQ = Key Question; OSDB = Obstructive Sleep-Disordered Breathing; RCT = Randomized, Controlled Trial

### Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

**Published Literature:** To ensure comprehensive retrieval of relevant studies, we will search MEDLINE® via PubMed, EMBASE, and the Cochrane Library. We will use the search strategy presented in Table 4 (initially conducted in July 2015), adapted as needed for each database. The final search strategies will be peer reviewed by an independent information specialist.

As noted, we will use date limits of January 1, 1980, to the present for the searches of indexed literature. We will also review the reference lists of both studies included in the report to identify relevant studies and recent systematic reviews on the topic.

We will conduct a final literature search update at the time of peer review of the draft report. We will screen and include relevant studies with each update. We will also incorporate relevant, eligible studies identified by peer reviewers or public commenters.

**Table 4. MEDLINE (PubMed) search strategy**

Search terms	Search results
1 tonsillectomy [mh] OR adenotonsillectomy OR tonsillotomy OR adenoidectomy	10158
2 therapeutics[mh] OR therapy[sh] OR "treatment outcome"[mh] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR therapeutics[tiab] OR outcome[tiab] OR outcomes[tiab] OR treatment[tiab] OR treatments[tiab] OR treatment* OR treat* OR intervention OR interven* OR surgical procedures, operative[mh] OR surgery[tiab] OR surgeries[tiab] OR surgical[tiab] OR manage[tiab] OR management[tiab] OR evaluate[tiab] OR evaluation[tiab] OR sleep[tiab] OR Anti-Inflammatory Agents [mh] OR Multi-Ingredient Cold, Flu, and Allergy Medications [mh] OR Respiratory System Agents [mh] OR Anti-Bacterial Agents [mh] OR antibiotic [tiab] OR Anti-Allergic Agents [mh]	11304977
3 palatine tonsil[mh] OR tonsil*[tiab] OR adenoids [mh] OR adenoid [tiab]	32464
4 Sleep Apnea Syndromes [mh] OR Pharyngitis [mh] OR Craniofacial Abnormalities [mh] OR tonsillitis [tiab] OR "sleep apnea" [tiab] OR "throat infection" [tiab] OR "sleep disordered breathing" [tiab] OR "down syndrome" [tiab]	103125
5 #3 AND (#1 OR #2)	20464
6 ((#4 AND #3) AND (#1 OR #2))	6026
7 #5 OR #6 OR #1	23407
8 #7 AND (child* OR adoles* OR pediater* OR young OR youth OR infant)	12142
9 #8 AND eng [la]	8854
10 #9 NOT newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR legal cases[pt] OR congresses[pt] OR review [pt]	6676
11 #10 AND 1980:2016[dp]	5897

Key: [la] language; [mh] medical subject heading; [pt] publication type; [tiab] title and abstract ;

**Grey Literature:** We will search government and regulatory agency web sites, including those for the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency (EMA), for information on drugs or devices used in tonsillectomy (see Appendix A for FDA approval information). We will search ClinicalTrials.gov and other trials registries for information about relevant ongoing trials and to confirm that we have obtained available publications of results from completed trials.

**Scientific Information Packets:** The Scientific Resource Center (SRC) will notify relevant stakeholders (including device manufacturers and pharmaceutical companies) about the opportunity to submit Scientific Information Packets (SIPs). Appendix A outlines manufacturers of key device and drugs used to treat the population of interest. We will compare the information in SIPs received with the biomedical literature and grey literature retrieval. We will apply the same inclusion criteria (Table 3) to studies identified via SIPs.

### Selecting Studies

**Screening forms:** We will develop forms for screening and preliminary data extraction. The form used at the abstract screening level will include basic questions to determine study eligibility based on the exclusion and inclusion criteria. The forms used for the full-

text screening level will include additional questions to identify studies that meet all the inclusion criteria. The forms will also include questions to assist in preliminary grouping of the eligible studies by KQ.

**Abstract screening:** We will review the titles and abstracts of all publications identified through our searches against our inclusion criteria. To be excluded, publication abstracts must be reviewed and excluded independently by two members of the investigative team. When differences between the reviewers arise, we will carry the article forward for full-text review.

**Retrieving and reviewing full-text articles:** We will retrieve and review all articles that meet our predetermined inclusion criteria from abstract screening or for which we have insufficient information to make a decision about eligibility. Two members of the team will independently review each article for eligibility. Differences between the reviewers will be adjudicated by a senior team member or via team discussion. We will use the same screening forms and inclusion criteria to assess eligibility of citations recommended by peer and public reviewers and for the literature retrieved by updated literature searches.

### **Data Extraction and Data Management**

We will develop a simple categorization scheme for coding the reasons that articles at full review are excluded. We will record exclusion codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database and will compile a list of excluded papers and exclusion reasons in the report. We will deposit data extracted into the Systematic Review Data Repository (SRDR).

We will create data extraction forms to collect detailed information on the study characteristics, intervention(s), comparator(s), arm details, reported outcomes and outcome measures, and our risk-of-bias assessment. We will pilot test the data entry forms.

For studies that meet the eligibility criteria from the full-text review assessment, we will extract, as appropriate:

- Study characteristics including study design, year, setting
- Population characteristics including age, race, ethnicity, BMI and growth information, and conditions such as Down Syndrome
- Operational definition of indication (OSDB or recurrent throat infection) for tonsillectomy, including information related to the documentation of infection such as diagnostic criteria; type of infection (streptococcal, viral, etc.); and number, timing, and severity of throat infections and information about sleep studies or methods to characterize OSDB
- Intervention and comparator(s) description and characteristics
- Outcomes of interest reported (Tables 2-3)
- Operational definition of each outcome
- Length of followup.

Tables 2 and 3 indicate the outcomes and harms of interest.

### **Assessment of Methodological Risk of Bias of Individual Studies**

We will evaluate the methodologic risk of bias (ROB) of individual studies using criteria and established tools described in the *Methods Guide for Effectiveness and*

*Comparative Effectiveness Reviews* as appropriate for each study design.<sup>26</sup> Two investigators will assess each included study independently. Disagreements will be resolved through discussion and/or via a senior investigator.

We will use prespecified questions (Table 4 in *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions*<sup>26</sup>) appropriate to each study design to assess risk of bias. We may also use questions included in the RTI Item Bank for observational studies.<sup>27</sup> We will use an adapted version of the McMaster Quality Assessment Scale of Harms tool to assess harms reporting.<sup>28</sup> We will enumerate the risk of bias assessments and sources of bias for all studies. We will describe risk of bias as “high,” “moderate,” or “low” using pre-established thresholds for risk of bias assessments.<sup>29</sup>

We will omit high risk of bias studies from analyses but will conduct sensitivity analyses to gauge their effects.

### **Data Synthesis**

We will provide a qualitative and quantitative synthesis of studies meeting our review criteria. In reporting results, we will give highest priority to patient-centered outcomes. Specific meta-analysis or meta-regression will depend on the data available. We will refine our analytic approach as we gather more data on the available literature. Our preferred approach, conditional on sufficient sources of evidence, is to combine studies using a hierarchical mixed effects model. Hierarchical random effects allow results from individual studies to be partially pooled, meaning that each study can contribute to inference in the meta-analysis without inappropriately assuming that the set of studies are identical. These random effects will allow us to estimate the overall (population) effect and the variance of the effect across studies, after controlling for available study-level covariates.

Quantifying study-level heterogeneity via random effects is preferable to using an arbitrary variance cutoff value or statistical tests for heterogeneity, such as Q statistics or  $I^2$  scores. The decision of whether to partially pool a set of studies using random effects depends not on how heterogeneous their outcomes are, but rather whether they can be considered exchangeable studies from a population of studies of the same phenomenon.<sup>30</sup> This should be determined based on the design and quality of the studies, independently of the studies' relative effect sizes.

We may account for some differences among study populations in the models by adjusting for factors such as age distribution, demographic attributes, and the underlying indications in the study sample. Newer approaches to random effects meta-analysis, such as Polya tree mixture models,<sup>31</sup> allow for robust (e.g., non-parametric) estimates of variation that do not rely on the assumption of normally-distributed random effects. This permits us to account for “outlier” studies in the meta-analytic model without either discarding them unnecessarily or allowing them to disproportionately influence meta-estimates. Additionally, publication bias can bias the distribution of outcomes away from a normal distribution.

We anticipate that we will encounter fundamental differences among classes of treatment (e.g., pharmacologic or surgical). Thus, we will use separate meta-analytic models for each type of intervention. We will also test the sensitivity of our meta-analytic

models to misclassification error or to pooling studies into classes that are too heterogeneous (i.e., too few classes in the set).

Analysis of subgroups will be done formally, within a statistical model, or by stratifying results. We will organize our report in such a way that we provide end-users with both overall outcomes data and information specific to subgroups defined by factors such as number of throat infections that can be easily identified and stand alone as needed. We will use subgroup analysis, when possible, to evaluate the intervention effect in a defined subset of the participants in a trial or in complementary subsets. Subgroup analysis can be undertaken in a variety of ways, from completely separate models at one extreme, to simply including a subgroup covariate in a single model at the other, with multilevel and random effects models somewhere in the middle. We would prefer to analyze subgroups via group-level covariates and random effects where possible, but recognize that the number and size of constituent studies can limit our ability to do so.

Meta-regression models describe associations between the summary effects and study-level data; that is, they describe only between-study and not between-patient variation. We will use multilevel models, which boost the power of the analysis by sharing strengths across subgroups for variables, where it makes sense to do so; alternatively, we will conduct subgroup analysis (with random effects meta-analysis) to explore heterogeneity when we have a sufficient number of studies. With fewer than 4 to 6 studies per group, estimating random effect variances without additional prior information is difficult.<sup>32</sup>

### **Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes**

We will use explicit criteria for rating the overall strength of the evidence for intervention-final outcome pairs. We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the ROB ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

We will assess strength of evidence as stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* updated strength of evidence chapter.<sup>29</sup> Current guidance on strength of evidence evaluation emphasizes the following major domains: study limitations (low, medium, high level of limitation), consistency (consistent, inconsistent, or unknown), directness (direct, indirect), precision (precise, imprecise), and reporting bias (suspected, undetected). Intervention-outcome pairs will be given an overall evidence grade based on the ratings for the individual domains.

The assessment of the study limitations domain will be derived from the ROB of the individual studies that addressed the KQ and specific outcome under consideration. The domains of consistency and precision will be assessed based on the direction and variation of the estimates. We will assess reporting bias of randomized controlled trials by examining outcomes of trials as reported in resources such as ClinicalTrials.gov to determine if prespecified outcomes are missing in the published literature.

We assign an overall grade (high, moderate, low, or insufficient) for the strength of evidence for each key outcome (Table 5). We determined outcomes of greatest clinical importance (Table 2) in consultation with the TEP and our content experts.

**Table 5. Strength of evidence grades and definitions**

<b>Grade</b>	<b>Definition</b>
<b>High</b>	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
<b>Moderate</b>	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
<b>Low</b>	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
<b>Insufficient</b>	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Two senior investigators will independently grade the body of evidence, with disagreements resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing results for each outcome. When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient. The full review team will review the final SOE determinations.

### **Assessing Applicability**

We will assess the applicability of findings reported in the included literature to the general population of children with OSDB or recurrent throat infections who are candidates for tonsillectomy. Specifically, we will determine the population, intervention, comparator, and setting in each study and develop an overview of these elements for each intervention category. We anticipate that areas in which applicability will be especially important to describe will include age, BMI, variability in definition or characterization of indication for tonsillectomy, and severity of indications or underlying conditions such as obesity.

### **V. References**

1. Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 2011 Jan;144(1 Suppl):S1-30. PMID: 21493257.
2. Parker NP, Walner DL. Trends in the indications for pediatric tonsillectomy or adenotonsillectomy. *Int J Pediatr Otorhinolaryngol* 2011 Feb;75(2):282-5. PMID: 21168225.
3. Patel HH, Straight CE, Lehman EB, et al. Indications for tonsillectomy: a 10 year retrospective review. *Int J Pediatr Otorhinolaryngol* 2014 Dec;78(12):2151-5. PMID: 25447951.
4. Wennberg J, Gittelsohn. Small area variations in health care delivery. *Science* 1973 Dec 14;182(4117):1102-8. PMID: 4750608.
5. Boss EF, Marsteller JA, Simon AE. Outpatient tonsillectomy in children: demographic and geographic variation in the United States, 2006. *J Pediatr* 2012 May;160(5):814-9. PMID: 22183449.
6. Georgalas CC, Tolley NS, Narula PA. Tonsillitis. *BMJ Clin Evid* 2014;2014PMID: 25051184.

7. Dooling KL, Shapiro DJ, Van Beneden C, et al. Overprescribing and inappropriate antibiotic selection for children with pharyngitis in the United States, 1997-2010. *JAMA Pediatr* 2014 Nov;168(11):1073-4. PMID: 25264869.
8. Bathala S, Eccles R. A review on the mechanism of sore throat in tonsillitis. *J Laryngol Otol* 2013 Mar;127(3):227-32. PMID: 23317998.
9. Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984 Mar 15;310(11):674-83. PMID: 6700642.
10. Paradise JL, Bluestone CD, Colborn DK, et al. Adenoidectomy and adenotonsillectomy for recurrent acute otitis media: parallel randomized clinical trials in children not previously treated with tympanostomy tubes. *JAMA* 1999 Sep 8;282(10):945-53. PMID: 10485679.
11. Paradise JL, Bluestone CD, Colborn DK, et al. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics* 2002 Jul;110(1 Pt 1):7-15. PMID: 12093941.
12. Teo DT, Mitchell RB. Systematic review of effects of adenotonsillectomy on cardiovascular parameters in children with obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2013 Jan;148(1):21-8. PMID: 23042843.
13. Walz PC, Schroeder JW, Jr. Pediatric polysomnography for sleep-disordered breathing prior to tonsillectomy: a guideline review. *Pediatr Ann* 2013 Oct;42(10):188-94. PMID: 24126980.
14. Marcus CL, Rosen G, Ward SL, et al. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics* 2006 Mar;117(3):e442-51. PMID: 16510622.
15. Prashad PS, Marcus CL, Maggs J, et al. Investigating reasons for CPAP adherence in adolescents: a qualitative approach. *J Clin Sleep Med* 2013;9(12):1303-13. PMID: 24340293.
16. Ramirez A, Khirani S, Aloui S, et al. Continuous positive airway pressure and noninvasive ventilation adherence in children. *Sleep Med* 2013 Dec;14(12):1290-4. PMID: 24157098.
17. Jambhekar SK, Com G, Tang X, et al. Role of a respiratory therapist in improving adherence to positive airway pressure treatment in a pediatric sleep apnea clinic. *Respir Care* 2013 Dec;58(12):2038-44. PMID: 23764862.
18. Beecroft J, Zanon S, Lukic D, et al. Oral continuous positive airway pressure for sleep apnea: effectiveness, patient preference, and adherence. *Chest* 2003 Dec;124(6):2200-8. PMID: 14665501.
19. Edmonson MB, Eickhoff JC, Zhang C. A population-based study of acute care revisits following tonsillectomy. *J Pediatr* 2015 Mar;166(3):607-12 e5. PMID: 25524315.
20. Gallagher TQ, Wilcox L, McGuire E, et al. Analyzing factors associated with major complications after adenotonsillectomy in 4776 patients: comparing three tonsillectomy techniques. *Otolaryngol Head Neck Surg* 2010 Jun;142(6):886-92. PMID: 20493363.
21. Dhiwakar M, Clement WA, Supriya M, et al. Antibiotics to reduce post-tonsillectomy morbidity. *Cochrane Database Syst Rev* 2012;12:CD005607. PMID: 23235625.
22. Chan DK, Parikh SR. Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope* 2014 Aug;124(8):1789-93. PMID: 24338331.
23. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).

24. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647. PMID: 25555855.
25. Treadwell JR, Singh S, Talati R, et al. A framework for best evidence approaches can improve the transparency of systematic reviews. *J Clin Epidemiol* 2012 Nov;65(11):1159-62. PMID: 23017634.
26. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD); 2008.
27. Viswanathan M, Berkman ND, Dryden DM, Hartling L. Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank. *Methods Research Report*. (Prepared by RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13-EHC106-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).
28. McMaster University Centre for Evidence-based Practice. McMaster Quality Assessment Scale of Harms (McHarm) for primary studies. Hamilton ON: McMaster University; 2008.
29. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol* 2014 Dec 20; PMID: 25721570.
30. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009 Jan;172(1):137-59. PMID: 19381330.
31. Branscum AJ, Hanson TE. Bayesian nonparametric meta-analysis using Polya tree mixture models. *Biometrics* 2008 Sep;64(3):825-33. PMID: 18162115.
32. A G. Prior distributions for variance parameters in hierarchical models. *Bayesian Analysis*. 2006;1(3):515-33.

## VI. Definition of Terms

- Tonsillectomy includes tonsillectomy, adenotonsillectomy, or partial tonsillectomy performed using any technique (cautery, dissection, etc.).
- Obstructive sleep-disordered breathing includes breathing difficulties during sleep as operationalized in each study in the review, including obstructive sleep apnea and upper airway resistance syndrome.
- Comparative effectiveness includes both the effectiveness and harms of interventions.
- Adjunctive perioperative pharmacologic agents refer to agents, such as steroids or antibiotics, given to attempt to reduce postoperative morbidity including pain or nausea and vomiting after surgery.
- Perioperative refers to the preoperative, intraoperative, and immediate postoperative (post-anesthesia care) periods.
- Postoperative refers to the period from discharge from post-anesthesia care to up to 10 days post-surgery.
- Primary bleeding is bleeding within the first 24 hours postoperatively. Secondary bleeding is bleeding more than 24 hours postoperatively.

## VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
12-3-2015	Section II, Table 2: PICOTS for KQ 5	PICOTS for KQ 5 do not specify pharmacologic agents of interest	We have revised the intervention in the PICOTS to include the following pharmacologic agents to address this question: anti-emetics, steroids, and NSAIDs. It has been revised to state: "Tonsillectomy plus adjunctive perioperative (i.e., preoperative, intraoperative, or immediate postoperative [post-anesthesia care] periods) pharmacologic agents, specifically anti-emetics, steroids and NSAIDs."	The evidence base includes many different medications, and combinations of medications, used perioperatively for pain or postoperative nausea and vomiting. This potentially can make synthesis challenging. To improve the relevance and usefulness of this key question, we have specified the intervention categories of interest to those most relevant for clinical practice. We consulted with our Task Order Officers (TOO) and partner representatives on the Technical Expert Panel (TEP) about limiting the focus of this KQ to 1) anti-emetics, 2) steroids, and 3) NSAIDs to keep the review targeted on key clinical dilemmas. Input from TEP members and TOOs suggested that this approach will best serve guideline developers, clinicians, and families who are making treatment decisions.
12-3-2015	Methods	We will register the review protocol in PROSPERO.	We have registered the review (CRD42015025600).	Provides registration details.

02-10-2016	Section IV, Table 3, Publication year	Publication year=1980-present for all KQ	Publication year for KQ 3-5=2000-present	<p>As noted previously, we are using a best evidence approach in this CER. As such, we have identified a sufficient literature base published after the year 2000 to address adequately and completely these research questions (KQ3-5). Of note, studies conducted prior to 2000 focus on either interventions that are no longer widely used in the US, or are of interventions for which there are adequate, newer studies of appropriate quality for review. We consulted with our TOOs and partner representatives on the TEP about this change. Feedback from partner representatives suggested that this change would not compromise the validity of the review's findings and is appropriate for developing a report that is not clouded by inappropriate inclusions.</p> <p>We will also include discussion of relevant prior systematic reviews that have included earlier studies in order to address key findings.</p>
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### VIII. Review of Key Questions

AHRQ posted the KQ on the Effective Health Care Website for public comment. The EPC refined and finalized the KQ after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the KQ are specific and relevant.

### 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 KQ for research that will inform healthcare 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 constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and 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 do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or 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. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer 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

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

## XIII. Role of the Funder

This project was funded under Contract No. HHS290201500003I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## **Appendix A. Pharmacologic Agents and Devices Used for Treatment of Children with Recurrent Throat Infections or Obstructive Sleep-Disordered Breathing**

### Pharmacologic Agents

Pharmacologic management of recurrent throat infection or obstructive sleep-disordered breathing may include use of the following classes of drugs:

**Anorexiant:** No medications are FDA-approved specifically for treating obesity in children. Orlistat may be prescribed off-label to post-pubertal adolescents.

**Antibiotics:** Antibiotics approved by the FDA specifically for treating streptococcal tonsillitis include amoxicillin, cephalexin, penicillin, azithromycin, clarithromycin, and cefuroxime. Other antibiotics such as cefaclor may be used off-label.

**Anti-inflammatory medications:** Over-the-counter non-steroidal anti-inflammatory medications such as naproxen, aspirin, celecoxib, or ibuprofen may be used to treat pain. Ketorolac is used extensively off-label for pain following pediatric surgeries.

**Antihistamines and decongestants:** These agents may be used singly or in combination and include diphenhydramine, chlorpheniramine, loratadine, fexofenadine, cetirizine, pseudoephedrine, phenylephrine, oxymetazoline. Some drugs are not recommended in younger children (e.g., diphenhydramine) as they may cause drowsiness.

**Leukotriene inhibitors:** These drugs are FDA-approved to treat asthma symptoms in children age 5 and older. Agents include montelukast and zafirlukast.

**Local anesthetics:** Local anesthetics such as bupivacaine may be instilled into the surgical area preoperatively or intraoperatively.

**Nasal steroids:** Several intra-nasal steroids are approved by the FDA for the treatment of seasonal allergy symptoms, generally in children more than 6 years of age. Agents include beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide.

**Opioid analgesics:** Opioid analgesics used after tonsillectomy include tramadol. Tramadol is not specifically FDA-approved for pediatric use, but it is used as a codeine alternative in pediatric tonsillectomy.

**Systemic steroids:** Systemic steroids may be used off-label to mitigate postoperative nausea and vomiting and include dexamethasone and methylprednisolone.

## Devices

Class I devices are FDA-exempt from premarket notifications. Ear, nose, and throat surgical devices include a variety of devices for surgical procedures to examine or treat the tonsils and other organs. Table A-1 lists the FDA Class I device categories that may be used in tonsillectomy.

**Table A-1. FDA Class I devices**

Product Code	Device	2015 Registrations <sup>a</sup>
KBM	Dissector Tonsil	51
KBO	Guillotine Tonsil	4
KBP	Hook Tonsil Suturing	12
KBQ	Knife Tonsil	37
KBR	Needle Tonsil Suturing	22
KBT	Punch Tonsil	21
KBX	Screw Tonsil	7
KBZ	Snare Tonsil	51
KCB	Tube Tonsil Suction	60

<sup>a</sup> Full listing of registered devices for 2015 can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm>. The FDA notes that device registration does not in any way denote approval of the establishment or its products by FDA.

**Table A-2. FDA 510K<sup>a</sup> approvals**

Product	Company	Decision Date	510(K) Number
Peak PlasmaBlade TNA Tonsil And Adenoid Tissue Dissection Device	Peak Surgical Inc.	6/5/2009	K083415
Karl Storz Ent Needles Tonsil Syringes & Needles	Karl Storz Endoscopy-America Inc.	5/9/1995	K951395
Karl Storz Nasal Tonsil Ear Laryngeal Snare	Karl Storz Endoscopy-America Inc.	4/6/1995	K951201
Tonsil Sponge Gauze Dissector Cylindrical Sponges	Medical Insights Inc.	4/14/1994	K940903
Tonsil Sponges	Mcneil Healthcare Inc.	1/31/1994	K935882
Tonsil Sponge X-Ray Detectable W/String	Bioseal	8/3/1988	K882709
Butcher Strung Tonsil Sponge	Ormed Mfg. Inc.	7/18/1988	K882529
Tape Strung Tonsil Sponge	Ormed Mfg. Inc.	7/18/1988	K882530
Stick Sponge Strung Tonsil Sponge Double Strung	American Silk Sutures Inc.	8/4/1987	K872806
13-290 Various Tonsil Scissors-Strully Yankauer	Artiberia	6/20/1985	K851762
Tonsil Knife-Variou	Premier Dental Products Co.	5/30/1984	K841005
Floret Tonsil & Adenoid Sponges	Ritmed Inc.	6/3/1983	K830264
Myle's Guillotine	Kelleher Corp.	8/30/1982	K822274
Tonsil Dissectors	Kelleher Corp.	8/24/1982	K822187
Tonsil Snares	Kelleher Corp.	8/24/1982	K822188
Tonsil Scissors 7	Conphar Inc.	5/28/1982	K821292
Tonsil Scissors Straight 5 1/2	Conphar Inc.	5/28/1982	K821294
Conphar Tonsil Scissors	Conphar Inc.	5/27/1982	K821361

Tonsil Sponges	Stan-Pak Ent.	2/4/1982	K820095
Sterile Tonsil Sponges	Medspec Corp.	10/10/1980	K802060
Frazier-Ferguson Suction Tubes	Edward Weck Inc.	8/12/1980	K801468

<sup>a</sup> 510K approval is premarket notification, which allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories.

**Table A-3. Additional devices (used for multiple surgeries or in multiple conditions)**

<b>Device</b>	<b>Manufacturer(s)</b>
<b>Ablative Devices</b>	
Coblator	Arthrocare
<b>Electrocautery Devices</b>	
Aaron 2250, 3250, PRO300, J-Plasma	Bovie Medical Corporation
Covidien Electrosurgery Generators	Covidien/Medtronic
<b>Laser</b>	
AccuPulse, VersaPulse, CO2	Lumenis
SP Dynamis, SP Spectro	Fotona
Diomax, Limax, MCO, MY60	KLS Martin
<b>Microdebrider</b>	
Straightshot Microdebrider	Medtronic
<b>Harmonic scalpel</b>	
HARMONIC Technology	Ethicon
<b>Other</b>	
CPAP	ResMed, Respironics, Fisher and Paykel, DeVilbiss, Somnetics, Aeiomed, ProBasics, Puritan Bennett, RespCare, Invacare, SleepNet, 3B Medical

Abbreviations: CPAP = Continuous Positive Airway Pressure