

# Evidence-based Practice Center Systematic Review Protocol

## Treatments for Seasonal Allergic Rhinitis

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

Seasonal allergic rhinitis (SAR), also known as hay fever, is an inflammatory condition of the upper airways that occurs in response to exposure to airborne allergens (typically tree, grass, and weed pollens) in sensitized individuals. Although there is geographic variability in the seasonal emergence of allergenic pollens across the United States, tree pollens tend to emerge in the spring, grass pollens in the summer, and weed pollens in the fall. SAR is distinguished from perennial allergic rhinitis (PAR), which is triggered by continuous exposure to house dust mites, animal dander, and other allergens generally found in an individual's indoor environment. Patients may have either SAR or PAR or both (i.e., PAR with seasonal exacerbations). Regardless of the inciting allergen(s), the four defining symptoms of allergic rhinitis are nasal discharge (rhinorrhea), nasal itching, sneezing, and/or nasal congestion. Many patients also experience symptoms of allergic conjunctivitis, such as itchy and watery eyes.<sup>1</sup> Treatment effectiveness is assessed by improvement of these symptoms and improved quality of life. In children, additional symptoms of rhinitis include the allergic salute (rubbing the hand against the nose in response to itching and rhinorrhea), allergic shiner (bruised appearance of the skin under one or both eyes), and allergic crease (a wrinkle across the bridge of the nose caused by repeated allergic salute).<sup>2-5</sup>

#### Classification

Traditionally, allergic rhinitis syndromes were categorized as SAR, PAR, and PAR with seasonal exacerbation.<sup>3</sup> This is the classification scheme we will use for our report. In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) international working group proposed a new classification scheme consisting of four categories based on rhinitis severity and duration: 1) mild intermittent, 2) mild persistent, 3) moderate/severe intermittent, and 4) moderate/severe persistent.<sup>6</sup> This new scheme suggests a stepwise treatment approach according to the severity and duration of symptoms.<sup>2</sup> However, the new scheme is not interchangeable with the traditional one, as different patient populations are defined by each.<sup>3,7</sup> In 2008, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) updated a Joint Task Force Practice Parameter on the diagnosis and management of rhinitis. The update retained the terms seasonal and perennial because "[t]hese traditional descriptive terms are clinically useful and allow for accurate categorization of the vast majority of patients."<sup>3</sup> For our report, we will search for trials involving patients with seasonal allergic rhinitis only.

#### Burden of Disease

SAR afflicts approximately 10 percent of the U.S. population, or 30 million individuals.<sup>8,9</sup> In 2009, 17.7 million U.S. adults (7.8%) were diagnosed with hay fever, and 7.2 million U.S.

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children (9.8%) reported having had hay fever in the previous 12 months.<sup>10,11</sup> The 2007 Pediatric Allergies in America survey revealed that 313 (62%) of 500 children (less than 18 years of age) diagnosed with allergic rhinitis had SAR. SAR has been demonstrated to adversely affect quality of life,<sup>12-14</sup> sleep,<sup>15,16</sup> cognition,<sup>17</sup> emotional life,<sup>18</sup> and school performance.<sup>19, 20</sup>

### Pathophysiology

Medications used to treat SAR target biochemical pathways that cause characteristic symptoms. SAR results from the binding of an inhaled aeroallergen to immunoglobulin E (IgE) on the surface of mast cells in the nasal mucosa. An early phase allergic response follows: Mast cell degranulation releases preformed inflammatory mediators, such as histamine and leukotrienes, which produce immediate nasal itching and sneezing. Histamine stimulation of the histamine-1 (H<sub>1</sub>) receptors on sensory nerves causes vascular dilation and increased plasma leakage. Stimulation of parasympathetic (cholinergic) nerve fibers by leukotrienes and other mediators causes mucus secretion from nasal glands. Leukotrienes also increase vascular permeability. The result is nasal discharge and congestion, which is maximal at 15 to 30 minutes. Four to 12 hours after allergen exposure, a late-phase allergic response may occur. The late-phase response consists primarily of nasal congestion and is mediated by the influx and activation of inflammatory T-cells and eosinophils.<sup>2,21,22</sup> Ongoing, prolonged allergen exposure and repeated late-phase responses lead to progressive inflammation of the nasal mucosa and increased allergen sensitivity. The amount of allergen capable of eliciting an allergic response lessens over time, an effect termed priming. The priming effect is thought to explain the development of mucosal hyper-responsiveness to nonallergen triggers, such as strong odors, cigarette smoke, and cold temperatures.<sup>21,23</sup> It also provides the rationale for initiating effective rhinitis therapies prophylactically before the commencement of pollen season.<sup>24,25</sup>

### Treatment

Treatments for allergic rhinitis comprise allergen avoidance, pharmacotherapy, and immunotherapy. For SAR, total allergen avoidance may be undesirable, as it may require limiting time spent outdoors. Thus, pharmacotherapy is preferable to allergen avoidance for symptom relief of SAR. Allergen-specific immunotherapy is the subject of a separate review, also sponsored by the Agency for Healthcare Research and Quality (AHRQ; research protocol available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=665&pageaction=displayproduct>).

Six classes of drugs and nasal saline are used to treat SAR. Several drugs have more than one route of administration (e.g., intranasal and oral), as described below.

1. Antihistamines used to treat allergic rhinitis target the H<sub>1</sub> receptor. Oral antihistamines are classified as selective and nonselective for H<sub>1</sub> receptors. Nonselective antihistamines (e.g., diphenhydramine) bind central H<sub>1</sub> receptors, which can cause sedation. They also bind cholinergic,  $\alpha$ -adrenergic, and serotonergic receptors, which can potentially cause other adverse effects such as dry mouth, dry eyes, urinary retention, constipation, and tachycardia. Nonselective antihistamines have been associated with impaired sleep, learning, and work performance and with motor vehicle, boating, and aviation accidents.<sup>26</sup> The selective antihistamines (e.g., loratadine), in contrast, are more specific for the H<sub>1</sub> receptor and do not

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cross the blood-brain barrier to bind central H<sub>1</sub> receptors. Adverse effects, such as sedation, are therefore reduced.<sup>27</sup> The choice of which antihistamine to use may be influenced by cost, insurance coverage, adverse effect profile, patient preference, and drug interactions.<sup>27</sup> All nonselective and some selective antihistamines are metabolized by hepatic cytochrome P450 enzymes. Plasma concentrations of these drugs are increased by cytochrome P450 inhibitors, such as macrolide antibiotics and imidazole antifungals.<sup>2</sup> Two intranasal antihistamines—azelastine and olopatadine—are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of SAR. Adverse effects of intranasal antihistamines may include a bitter aftertaste.

2. Corticosteroids are potent anti-inflammatory molecules. Intranasal corticosteroids are recommended as first-line treatment for moderate/severe or persistent allergic rhinitis.<sup>3,28</sup> However, whether they are superior to or equally effective as intranasal antihistamines for the relief of nasal congestion is uncertain,<sup>29,30</sup> particularly in patients with mild allergic rhinitis. Many preparations with differing pharmacokinetic and pharmacodynamic profiles exist. These can be used continuously (daily) during allergy season or as needed. It is not clear which approach is more effective in which patients or how benefits balance against potential adverse effects. Potential safety concerns relate to the risk of systemic corticosteroid absorption and include adrenal suppression, bone fracture among the elderly, and reduced bone growth and height in children. Adverse local effects may include nosebleeds, stinging, burning, and dryness. Aqueous formulations and proper technique may help to relieve these effects. Little is known about cumulative corticosteroid effects in patients who take concomitant oral or inhaled formulations for other diseases. For patients with persistent symptoms, it also is unclear whether adding oral or intranasal antihistamine to intranasal corticosteroid provides any additional benefit. Oral corticosteroids are occasionally prescribed for short courses (5 to 7 days) as needed in patients with severe symptoms unresponsive to other treatments.<sup>3</sup> Because there is no alternative to this specific use of corticosteroids in SAR, oral corticosteroids will not be reviewed in this report. Similarly, although FDA approved for SAR, intramuscular corticosteroid injections are not recommended for the treatment of SAR<sup>28</sup> and will not be reviewed in this report.
3. Decongestants are  $\alpha$ -adrenergic agonists that produce vasoconstriction. In the nasal mucosa, this results in decreased edema and nasal congestion. Intranasal decongestants (e.g., oxymetazoline) are often administered before an intranasal corticosteroid or an intranasal antihistamine to increase delivery of these drugs. Rebound congestion and symptom worsening (rhinitis medicamentosa) may occur with several days of use, although the exact interval is unknown. Other local adverse effects may include nosebleeds, stinging, burning, and dryness. Oral decongestants (e.g., phenylephrine, pseudoephedrine) are used alone and often are found in combination products marketed for the relief of colds and sinus congestion. Because pseudoephedrine is a key ingredient used for illicit methamphetamine production, its sale in the United States is restricted, resulting in the substitution of phenylephrine for pseudoephedrine in many cold and cough remedies. Systemic adverse effects of decongestants may include hypertension, irritability, tachycardia, dizziness, insomnia, headaches, anxiety, sweating, and tremors.<sup>2,31</sup> Decongestants are used with

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caution, if at all, in patients with diabetes mellitus, ischemic heart disease, unstable hypertension, prostatic hypertrophy, hyperthyroidism, and narrow-angle glaucoma. Oral decongestants are contraindicated with coadministered monoamine oxidase inhibitors and in patients with uncontrolled hypertension or severe coronary artery disease.<sup>25</sup>

4. Ipratropium is an anticholinergic agent that blocks parasympathetic nerve conduction and the production of glandular secretions within the nasal mucosa. Ipratropium nasal spray is approved by the FDA for treating rhinorrhea associated with SAR. Postmarketing experience suggests that there may be some systemic absorption; it is unclear whether this issue has been addressed in the peer-reviewed literature. Cautious use is advised for patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, particularly if another anticholinergic is coadministered by another route. Local adverse effects may include nosebleeds and nasal and oral dryness. Efficacy and safety beyond 3 weeks in patients with SAR have not been established.<sup>32</sup>
5. Intranasal mast cell stabilizers, including cromolyn, inhibit the antigen-induced release of inflammatory mediators from mast cells. These drugs are commonly administered prophylactically, before an allergic reaction is triggered, during a loading period in which they are applied four times daily for several weeks. Systemic absorption is minimal. Local adverse effects may include nasal irritation, sneezing, and an unpleasant taste.<sup>2,31</sup>
6. Cysteinyl leukotrienes are biological inflammatory mediators. Leukotriene receptor antagonists are oral medications that reduce allergy symptoms by inhibiting inflammation. Montelukast is the only leukotriene receptor antagonist approved by the FDA for the treatment of SAR. Potential adverse effects include upper respiratory tract infection and headache.<sup>31</sup>

### **Nasal Saline**

A 2007 Cochrane review provides evidence that nasal saline is beneficial in treating nasal SAR symptoms.<sup>33</sup> Because it is associated with few adverse effects, nasal saline may be particularly well suited for treating SAR symptoms during pregnancy, in children, and in those whose treatment choices are restricted due to comorbidities, such as hypertension and urinary retention.

### **Pregnancy**

The optimal treatment of SAR during pregnancy is unknown. Drugs that were effective before pregnancy may be effective during pregnancy, but their use may be restricted because of concerns about maternal and fetal safety. Because pregnancy is often an explicit exclusion criterion for clinical trials, data demonstrating efficacy and maternal and fetal safety are lacking for most drugs, including those used for SAR. Decisions about which treatments are best during pregnancy must weigh the potential treatment-related risks and benefits to both mother and fetus against the potential risks and benefits of enduring the symptoms of the disease. Drugs used to treat SAR are pregnancy category B (presumed safe based on animal studies but without adequate human data) or category C (of uncertain safety, with no demonstrated adverse effects in

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animals or humans). The risk of congenital malformation is greatest during organogenesis in the first trimester. If medication cannot be avoided during this time, intranasal treatments with minimal systemic effects, such as intranasal cromolyn (pregnancy category B) and nasal saline, are preferred.<sup>3</sup> Of the intranasal corticosteroids, only intranasal budesonide is category B; the others are category C. The safety of intranasal decongestants during pregnancy has not been studied. Pregnancy category B oral medications that may be considered for use after the first trimester include the selective antihistamines loratadine, cetirizine, and levocetirizine and several nonselective antihistamines. Oral decongestants are generally avoided during pregnancy, especially during the first trimester. The leukotriene receptor antagonist, montelukast, is pregnancy category B.

### Children

Most pharmacologic treatments for SAR are approved for use in adults and adolescents older than 12 years of age. For children, toddlers, and infants, treatment choices are increasingly limited due to safety concerns. Thus, optimal treatments for these age groups have been difficult to identify. For children who are able and willing to use intranasal medication, nasal saline presents a treatment choice with few potential adverse events. Similarly, intranasal cromolyn is approved for use in children older than 2 years of age. Although approved for use in children as young as 2 years of age, intranasal corticosteroids (e.g., fluticasone, mometasone, and triamcinolone) may be associated with potential adverse events resulting from systemic absorption, such as impaired bone growth, reduced height, suppression of the adrenal axis, hyperglycemia, and weight gain.

Children with occasional symptoms may be treated with antihistamines on days when symptoms are present or expected. Carbinoxamine is a nonselective antihistamine approved for use in infants. The selective antihistamines loratadine, desloratadine, and cetirizine are approved by the FDA for use in children older than 2 years of age. Intranasal antihistamines are approved for children older than 5 (azelastine) or older than 12 (olopatadine) years of age. In children older than 6 years of age, oral decongestants generally have few adverse effects at age-appropriate doses. However, in infants and young children, the use of oral decongestants may be associated with agitated psychosis, ataxia, hallucinations, and death.<sup>3</sup> Extended-release formulations are not recommended for children younger than 12 years of age.

### Rationale for Review

Multiple guidelines for the treatment of allergic rhinitis exist.<sup>3,25,28,34-37</sup> Although these guidelines generally support the use of intranasal corticosteroids as first-line treatment of moderate/severe SAR, the guidelines are not consistently based on systematic reviews of the literature and often do not address the treatment of SAR in children and pregnant women. Additionally, for mild SAR, agreement is lacking about whether intranasal or oral antihistamine, oral leukotriene receptor antagonist, or short-course intranasal or oral decongestant is first-line treatment. For both mild and moderate/severe SAR, the comparative effectiveness and safety of SAR treatments used in combination with each other are unknown. Uncertainty also exists about the effectiveness of as-needed compared to daily dosing and about the effect of SAR treatments on symptoms that often co-occur (i.e., eye symptoms and asthma symptoms). Our review aims to address these aspects of treatments for SAR.

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## II. The Key Questions

### Question 1

What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents ( $\geq 12$  years of age) with mild or with moderate/severe seasonal allergic rhinitis (SAR)?

- How does effectiveness vary with long-term (months) or short-term (weeks) use?
- How does effectiveness vary with intermittent or continuous use?
- For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
- For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

### Question 2

What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents ( $\geq 12$  years of age)?

- How do adverse effects vary with long-term (months) and short-term (weeks) use?
- How do adverse effects vary with intermittent or continuous use?

### Question 3

For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

- How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
- How do effectiveness and adverse effects vary with intermittent or continuous use?

### Question 4

For the subpopulation of children ( $< 12$  years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

- How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
- How do effectiveness and adverse effects vary with intermittent or continuous use?

## Summary of Public Comments

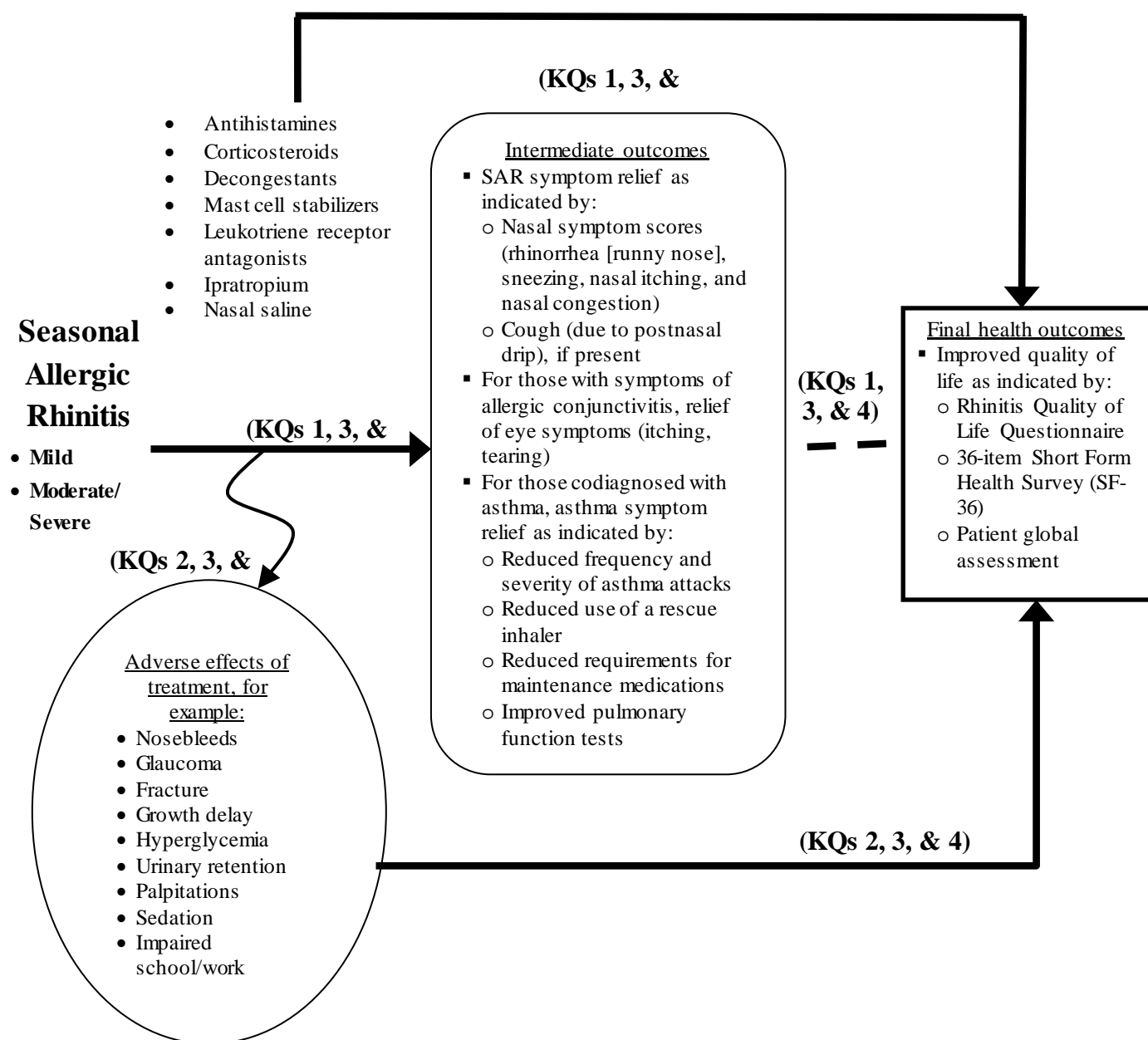
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The Key Questions (KQs) were posted for public comment for 4 weeks. Public comments consisted of the suggestion to add one additional drug comparator, clemastine, which was added to the intervention list.

### III. Analytic Framework

Figure 1. Analytic framework



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Abbreviations: KQs = key questions

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## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies in the Review

Selection criteria were developed with input from the expert clinicians and stakeholders of the Technical Expert Panel.

### Key Question 1—Comparative Effectiveness of Treatments in Adults 12 Years of Age or Older

The focus of this review is the comparison of effectiveness across six pharmacologic classes of treatments for SAR and nasal saline. Antihistamines are further classified into nonselective and selective subclasses, as shown in Table 1.

**Table 1. Pharmacologic treatments of seasonal allergic rhinitis**

Drug Class	Oral	Intranasal
H1-antihistamine		
• Nonselective	✓	✓
• Selective	✓	✓
Corticosteroid	✓*	✓
Chromone		✓
Leukotriene antagonist	✓	
Sympathomimetic decongestants	✓	✓
Anticholinergic (ipratropium bromide)		✓

\*Oral corticosteroids are not reviewed in this report.

Within a pharmacologic class, previous comparative effectiveness reviews have found insufficient evidence to support superior effectiveness of any single drug.<sup>3,28,35,38-44</sup> Thus, the focus of the review is across-class treatment comparisons. Within-class comparisons are made when multiple routes of administration are available for a single drug class (e.g., intranasal vs. oral selective antihistamines, intranasal vs. oral sympathomimetic decongestants). Expert guidance was sought to identify drug class comparisons that are most relevant for treatment decisionmaking. The checked boxes in Table 2 indicate the treatment comparisons identified. Reasons most often cited for not including a specific comparison were differential efficacy for specific SAR symptoms (e.g., intranasal anticholinergic [ipratropium] treats rhinorrhea vs. intranasal sympathomimetic decongestants treat nasal congestion) and noncomparable indications (e.g., intranasal antihistamines for long-term use vs. intranasal sympathomimetic decongestants for short-term use).

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**Table 2. Monotherapy and combination treatment comparisons reviewed for adults: Key Questions 1 and 2\***

	AH <sub>1</sub> -nS, oral	AH <sub>1</sub> -S, oral	AH <sub>1</sub> -S, nasal	CS, nasal	SD, oral	SD, nasal	C, nasal	LRA, oral	AC, nasal	NS
AH <sub>1</sub> -nS, oral		✓								
AH <sub>1</sub> -S, oral			✓	✓	✓		✓	✓	✓	✓
AH <sub>1</sub> -S, nasal				✓	✓			✓	✓	✓
CS, nasal							✓	✓	✓	✓
SD, oral										
SD, nasal										
C, nasal										
LRA, oral										
AC, nasal										
NS										
AH <sub>1</sub> -S, oral + CS, nasal		✓		✓						
AH <sub>1</sub> -S, oral + SD, oral		✓								
AH <sub>1</sub> -S, nasal + CS, nasal			✓	✓						

\*The top portion of this table is a grid of monotherapy treatment comparisons included in this review (✓).

The lower portion of the table indicates combination treatment comparisons included in this review (✓).

Abbreviations: AC = anticholinergic; AH<sub>1</sub>-nS = antihistamine, non-selective; AH<sub>1</sub>-S = antihistamine, selective; C = chromone; CS = corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline; SD = sympathomimetic decongestant

For the treatment comparisons identified, head-to-head randomized controlled trials (RCTs) are preferred; uncontrolled studies are prone to increased risk of bias due to the subjective reporting of both efficacy outcomes and adverse events in SAR research. The most informative (highest quality) RCTs are blinded, have a minimum treatment exposure of 2 weeks, and administer FDA-approved doses of SAR treatments to symptomatic patients during the allergen season. These trials comprise the highest level evidence for treatment effectiveness. For comparisons that do not have data from RCTs, observational study designs will be considered. Inclusion criteria for these studies are:

- One of the following designs:
  - Quasi-RCTs (crossover trials, before/after trials, open-label extensions, etc.)
  - Controlled (nonrandomized) clinical trials
  - Population-based comparative cohort studies
  - Case-control studies
- Each study must compare two drug classes directly.
- Confounders are controlled; for example, baseline asthma prevalence and severity are documented, pollen counts are documented in multicenter studies
- Detection bias is addressed through the use of any of these: blinding of outcome assessors or blinding of patients or clinicians to treatment allocation

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For all studies, disease will be limited to SAR. Outcomes must include patient-reported symptom scores and/or validated quality-of-life instruments; for comorbid asthma symptoms, pulmonary function tests are also required. Ideally, results for patients with moderate/severe symptoms will be presented separately from results for patients with mild symptoms. RCTs that do not separate results by symptom severity may be considered for inclusion if the body of evidence for a given comparison is sparse. Definitions of symptom severity will be adapted from the Allergic Rhinitis in Asthma (ARIA) guidelines.<sup>6</sup> ARIA defines mild SAR as lack of sleep disturbance, impairment of daily or leisure activities, impairment of school or work, or troublesome symptoms. Moderate/severe SAR is characterized by one or more of these disturbances. The following symptom rating scale is commonly used in SAR clinical trials<sup>45</sup>:

- 0 = Absent symptoms (no sign/symptom evident)
- 1 = Mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = Moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = Severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Results of existing systematic reviews and meta-analyses will be incorporated into the report if they assess relevant treatment comparisons, report at least one outcome of interest, and are of high quality. Quality will be assessed by two independent reviewers with tools recommended in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (e.g., the Assessment of Multiple Systematic Reviews [AMSTAR] tool).<sup>46</sup> Reference lists of RCTs, systematic reviews, and other reviews will be hand searched to confirm that all relevant RCTs have been identified. These selection criteria are summarized in Table 3.

**Table 3. Key Question 1: Comparative effectiveness of treatments—study inclusion criteria**

Category	Inclusion Criteria
Population	<ul style="list-style-type: none"> <li>• Individuals with SAR <ul style="list-style-type: none"> <li>◦ Mild symptoms</li> <li>◦ Moderate/severe symptoms</li> </ul> </li> <li>• Age 12 or older</li> <li>• May also have <ul style="list-style-type: none"> <li>◦ Comorbid eye symptoms</li> <li>◦ Comorbid asthma</li> </ul> </li> </ul>
Interventions/Comparators	Identified comparisons of pharmacologic treatments of SAR alone and in combination with each other (see Table 2) administered for at least 2 weeks
Outcomes	<ul style="list-style-type: none"> <li>• Nasal symptom scores</li> <li>• Cough</li> <li>• Eye symptom scores</li> <li>• Asthma outcomes <ul style="list-style-type: none"> <li>◦ Frequency of asthma attacks</li> <li>◦ Use of rescue medication</li> <li>◦ Maintenance medication dose</li> <li>◦ Pulmonary function tests</li> </ul> </li> <li>• Rhinitis Quality of Life Questionnaire</li> </ul>

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	<ul style="list-style-type: none"> <li>• 36-item Short Form Health Survey (SF-36)</li> <li>• Patient global assessment (PGA)</li> </ul>
Time Period	Minimum 2-week duration of treatment exposure
Setting	Outpatients during the pollen season
Study designs	<ul style="list-style-type: none"> <li>• RCTs with active comparator preferred <ul style="list-style-type: none"> <li>◦ Outcomes for patients with mild symptoms and with moderate/severe symptoms reported separately</li> <li>◦ Combined outcome reporting may be considered</li> </ul> </li> <li>• For identified comparisons with no RCT data, observational data will be considered. Inclusion criteria for observational data are: <ul style="list-style-type: none"> <li>◦ One of the following designs: <ul style="list-style-type: none"> <li>▪ Quasi-RCTs (crossover trials, before/after trials, open-label extensions, etc.)</li> <li>▪ Controlled (nonrandomized) clinical trials</li> <li>▪ Population-based comparative cohort studies</li> <li>▪ Case-control studies</li> </ul> </li> <li>◦ Each study must compare two drug classes directly.</li> <li>◦ Confounders are controlled; for example, baseline asthma prevalence and severity are documented, pollen counts are documented in multicenter studies</li> <li>◦ Detection bias is addressed through the use any of these: blinding of outcome assessors or blinding of patients or clinicians to treatment allocation</li> </ul> </li> <li>• Systematic reviews and meta-analyses <ul style="list-style-type: none"> <li>◦ Assess relevant treatment comparisons</li> <li>◦ Report at least one outcome of interest</li> <li>◦ High quality</li> </ul> </li> </ul>
Follow-up duration	Unrestricted
Sample size	Unrestricted

## Key Question 2—Comparative Adverse Effects of Treatments in Adults 12 Years of Age or Older

Comparative adverse effects reported in the RCTs, systematic reviews, meta-analyses, and observational studies identified for KQ 1 will be included. Additionally, systematic reviews and meta-analyses that specifically assess adverse events associated with treatment comparisons of interest will be sought. Table 4 lists systemic and local adverse effects of interest. Of particular interest are adverse effects associated with long-term treatment exposures where allergen seasons are of longer duration (e.g., in certain parts of the United States). For these adverse effects, comparative clinical trials of at least 300 patients evaluated for 6 months or 100 patients evaluated for at least 1 year will be included, according to FDA draft guidance for industry.<sup>45</sup>

**Table 4. Key Question 2: Systemic and local adverse effects of seasonal allergic rhinitis treatments**

<ul style="list-style-type: none"> <li>• Intranasal corticosteroids <ul style="list-style-type: none"> <li>◦ Systemic effects: adrenal suppression, hyperglycemia, bone demineralization/fracture, growth delay in children</li> <li>◦ Local effects: increased intraocular pressure, cataract formation, nasal septal atrophy, fungal infection, nosebleeds, stinging, burning, dryness, smell and taste abnormalities</li> </ul> </li> <li>• Selective and nonselective antihistamines <ul style="list-style-type: none"> <li>◦ Systemic effects: sedation, impaired school/work performance, traffic accidents</li> <li>◦ Local effects: stinging, burning, dryness, bitter aftertaste</li> </ul> </li> </ul>
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- Sympathomimetic decongestants
  - Systemic effects: hypertension, palpitations, insomnia, anxiety
  - Local effects: nosebleeds, stinging, burning, dryness, rhinitis medicamentosa
- Leukotriene receptor antagonists
  - Systemic effect: headache
- Anticholinergic, mast cell stabilizer, and nasal saline
  - Local effects: nosebleeds, stinging, burning, dryness

### Key Question 3—Comparative Effectiveness and Adverse Effects of Treatments in Pregnant Women

Treatment comparisons of interest include pregnancy category B oral and topical (intranasal) preparations, especially nasal saline. These are presented in Table 5. Oral sympathomimetic decongestants and intranasal antihistamines are pregnancy category C and are not included in this KQ.

Because pregnancy is commonly an exclusion criterion for participation in pharmaceutical RCTs, additional study designs in pregnant women with SAR (i.e., observational data, systematic reviews, and meta-analyses) will be considered for KQ 3. The inclusion criteria for these study designs are the same as for KQ 1.

In this report, adverse fetal effects associated with treatments for SAR in pregnant women is not identified as a target adverse event because these may be unreliably reported (i.e., not systematically collected or attributed). Therefore, when information about adverse fetal effects is available, this information will be discussed in the narrative portion of the report only rather than pooled.

**Table 5. Monotherapy and combination treatment comparisons reviewed for pregnant women: Key Question 3\***

	AH <sub>1</sub> -nS, oral <sup>†</sup>	AH <sub>1</sub> -S, oral <sup>‡</sup>	CS, nasal <sup>§</sup>	SD, nasal	C, nasal	LRA, oral	AC, nasal	NS
AH <sub>1</sub> -nS, oral <sup>†</sup>		✓	✓					
AH <sub>1</sub> -S, oral <sup>‡</sup>			✓		✓	✓		✓
CS, nasal <sup>§</sup>					✓	✓		✓
SD, nasal						✓		
C, nasal						✓		✓
LRA oral								
AC, nasal								
NS								
AH <sub>1</sub> -nS, oral <sup>†</sup> + NS	✓		✓					✓
AH <sub>1</sub> -S, oral <sup>‡</sup> + NS		✓						✓

\* The top portion of this table is a grid of monotherapy treatment comparisons included in this review (✓). The lower portion of the table indicates combination treatment comparisons included in this review (✓).

<sup>†</sup> Pregnancy category B oral nonselective antihistamines are cyproheptadine, dexchlorpheniramine, and diphenhydramine.

<sup>‡</sup> Pregnancy category B oral selective antihistamines are cetirizine and loratadine.

<sup>§</sup> Of the intranasal corticosteroids, only budesonide is pregnancy category B.

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Abbreviations: AC = anticholinergic; AH<sub>1</sub>-nS = nonselective antihistamine; AH<sub>1</sub>-S = selective antihistamine; C = chromone; CS = corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline; SD = sympathomimetic decongestant

## Key Question 4— Comparative Effectiveness and Adverse Effects of Treatments in Children Younger than 12 Years of Age

The population of interest is children younger than 12 years of age who have SAR. Identified treatment comparisons of interest for KQ 4 are presented in Table 6. Because of concerns about the use of sympathomimetic decongestants in children, oral and nasal preparations are not included. Similarly, intranasal anticholinergic (ipratropium) is not included because technical experts indicated that this drug is rarely used in children younger than 12 years of age. Potential comparative harms of intranasal corticosteroids in this population (reduced bone growth and height) are of particular interest. Comparative effect on school performance in school-age children is an additional key outcome.

Selection criteria are the same as in KQ1; that is, RCTs are the preferred study type. For identified comparisons that do not have RCT data, observational study designs will be considered. Inclusion criteria for RCTs, observational studies, systematic reviews, and meta-analyses are as outlined in Table 3, with the exception that the study population must be younger than 12 years old. Studies that report results for adults and children together may be considered for inclusion if the body of evidence for a given comparison is sparse.

**Table 6. Monotherapy and combination treatment comparisons reviewed for children younger than 12 years of age: Key Question 4\***

	AH <sub>1</sub> -nS, oral	AH <sub>1</sub> -S, oral	AH <sub>1</sub> -S, nasal	CS, nasal	C, nasal	LRA, oral	NS
AH <sub>1</sub> -nS, oral		✓	✓	✓		✓	
AH <sub>1</sub> -S, oral			✓	✓	✓	✓	
AH <sub>1</sub> -S, nasal				✓	✓	✓	
CS, nasal					✓	✓	✓
C, nasal						✓	✓
LRA, oral							
NS							
AH <sub>1</sub> -S, oral + SD, oral		✓		✓			
AH <sub>1</sub> -S, oral + CS, nasal		✓	✓	✓			

\* The top portion of this table (above the dark line) is a grid of monotherapy treatment comparisons included in this review (✓). The lower portion of the table indicates combination treatment comparisons included in this review (✓).

## Grey Literature

Grey literature will be sought by searching the FDA Web site, conference abstracts of relevant professional organizations (e.g., AAAAI, the British Society for Allergy and Clinical Immunology [BSACI]), and the clinical trial registries of the U.S. National Institutes of Health (ClinicalTrials.gov) and the World Health Organization. Scientific Information Packets provided by product manufacturers will be evaluated to identify unpublished trials that meet inclusion criteria.

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## B. Search Strategies

Search strategies will be developed by an expert librarian in collaboration with the project team and peer reviewed. Comprehensive literature searches of the following databases will be performed:

- MEDLINE<sup>®</sup> (PubMed<sup>®</sup> and Ovid)
- EMBASE<sup>®</sup> (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL)

For systematic reviews, the following databases will be searched:

- Cochrane Database of Systematic Reviews
- Database of Abstracts and Reviews of Effects (DARE) and the Health Technology Assessment (HTA) databases of the Centre for Reviews and Dissemination

Articles will be limited to those published in the English language. Technical experts advised that the majority of the literature on this topic is published in English. For additional details on search strategies, please see Appendix A. The MEDLINE search presented there will be adapted for other databases.

## C. Data Abstraction and Data Management

Search results will be transferred to EndNote<sup>®</sup> (Thomson Reuters, Philadelphia, PA) and subsequently into DistillerSR (Evidence Partners Inc., Manotick, ON, Canada) for selection. Using the study-selection criteria for screening titles and abstracts, each citation will be marked as: 1) eligible for review as full-text articles; 2) ineligible for full-text review; or 3) uncertain. A first-level title screen will be performed by one senior and one junior team member. Discrepancies will be decided through discussion and consensus. A second-level abstract screen will be conducted in duplicate manner by senior and junior team members according to defined criteria. For additional citations identified through subsequent literature searches, combined title and abstract screening will be performed by senior and junior team members as described. Inclusion and exclusion will be decided by consensus opinion; a third reviewer will be consulted if necessary. A training set of 25 to 50 abstracts will be examined initially by duplicate team members to assure uniform application of screening criteria. Full-text review will be performed when it is unclear whether selection criteria have been satisfied.

Full-text articles will be reviewed in the same fashion to determine their inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, will be kept in the DistillerSR database.

Data abstraction will be performed directly into tables created in DistillerSR with elements defined in an accompanying data dictionary. A training set of five articles will be abstracted by all team members who are abstracting data. All data abstraction will be verified with fact checking to confirm the accuracy of data entry. Abstracted data will be transferred from

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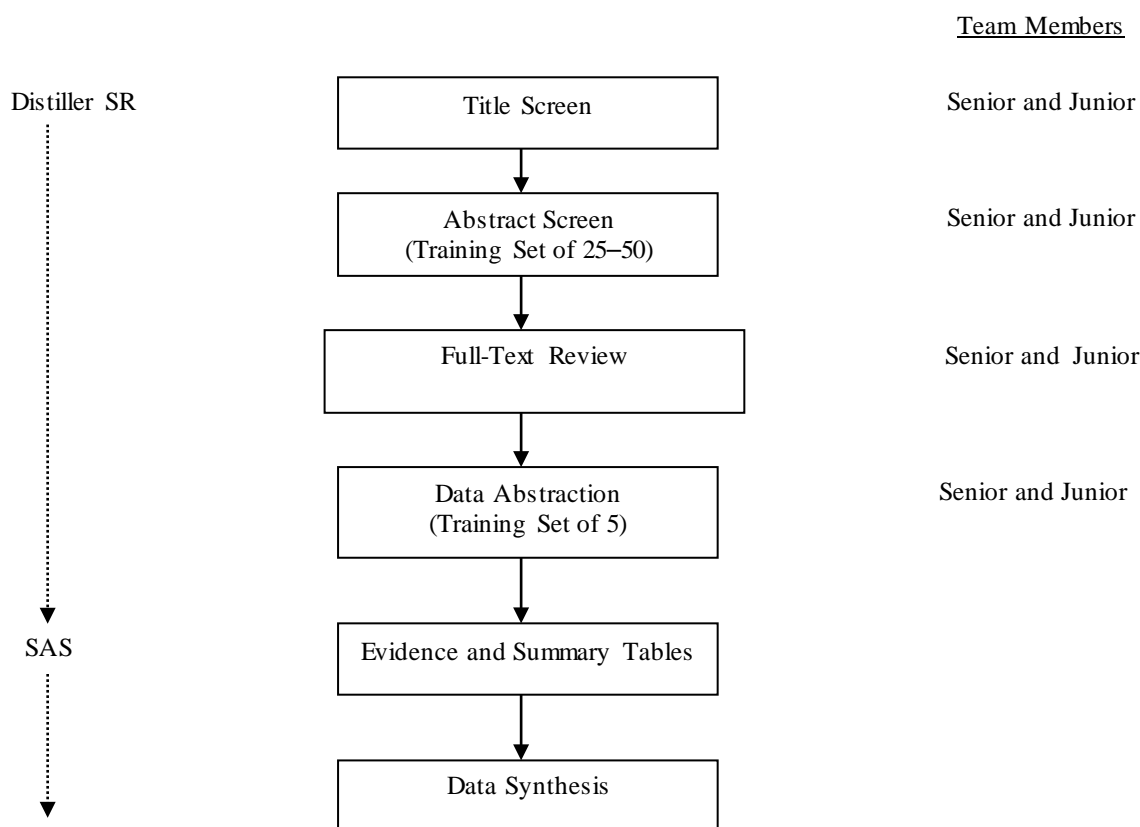
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DistillerSR to statistical management software, such as SAS (SAS Institute Inc., Cary, NC), to compile study-level and summary tables for inclusion in the report.

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**Figure 2. Schematic for data management and abstraction**



A complete set of data to be extracted will be developed during the abstraction phase. Some anticipated elements include, but are not limited to, the following: author, study year, enrollment dates, center(s), funding agency, blinding, numbers of patients, age, disease severity, intervention, outcome instrument(s), adverse events, and results.

## D. Assessment of Methodological Quality of Individual Studies

In adherence with the AHRQ *Methods Guide*,<sup>47</sup> criteria of the U.S. Preventive Services Task Force<sup>48</sup> will be applied to assess the quality of individual RCTs and cohort studies. The quality of abstracted studies will be assessed by two independent reviewers. Ratings of good, fair, and poor will be assigned (detailed in Appendix B). Other included observational studies will be assessed based on a selection of items proposed by Deeks and colleagues<sup>49</sup> (detailed in Appendix C) to inform the U.S. Preventive Services Task Force approach. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.

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Quality of incorporated systematic reviews and meta-analyses will be assessed by two independent reviewers with tools recommended in the AHRQ *Methods Guide* (e.g., the Assessment of Multiple Systematic Reviews [AMSTAR] tool).<sup>46</sup>

## E. Data Synthesis

Evidence for the effectiveness and safety of each treatment comparison will be summarized in narrative text. The decision to incorporate formal data synthesis into this review will be made after completing the formal literature search. Pooling of treatment effects will be considered for each treatment comparison according to AHRQ guidance.<sup>50,51</sup> If clinically and methodologically similar studies (i.e., studies designed to ask similar questions about treatments in similar populations and to report similarly defined outcomes) are available in sufficient number, results may be pooled. The pooling method will involve inverse variance weighting and a random-effects model. For any meta-analysis performed, we will assess clinical diversity in individual studies by using subgroup and sensitivity analyses. We will assess statistical heterogeneity by using Cochran's Q statistic and the  $I^2$  statistic. If we find considerable statistical heterogeneity, we will explore it by performing subgroup analysis, sensitivity analysis, and meta-regression if possible. Study level variables that will be considered include study quality (risk of bias assessment), specific drugs studied for across-class comparisons, and covariates, such as inclusion of asthma patients or use of rescue or ancillary medications. Outcomes of interest pertain directly to patients' experience of improvement in symptoms and quality of life, as recommended by Key Informants and the Technical Expert Panel.

## F. Grading the Evidence for Each Key Question

Our determination of the strength of the body of evidence will be based on the Evidence-based Practice Center (EPC) approach, which is similar to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.<sup>50,51</sup> Four main domains to be assessed are risk of bias, consistency, directness, and precision. Additional domains (dose-response association, strength of association, and publication bias) will be considered for assessment when these are relevant. For each treatment comparison of interest, the body of evidence will be evaluated separately to derive a single GRADE of high, moderate, low, or insufficient evidence. Evaluations will be conducted by two reviewers and agreement reached through discussion and consensus when necessary.

The GRADE definitions are as follows:

- **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 effect and may change the estimate.
- **Low:** low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

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- **Insufficient:** evidence either is unavailable or does not permit a conclusion.

## G. Assessing Applicability

The objective of this review is to provide an evidence-based understanding of the comparative effectiveness of available treatments for SAR. Populations of interest are children, adolescents, and adults (including pregnant women) who are experiencing mild or moderate/severe SAR symptoms. In this context, applicability is defined as the extent to which treatment effects observed in published studies reflect expected results when treatments are applied to these populations in the real world.<sup>52,53</sup>

Potential factors that may affect the applicability of the evidence for the KQs include:

- Underrepresentation of populations of interest, especially pregnant women
- Selection of patients with predominantly severe symptoms
- Dosage of comparator interventions are not reflective of current practice
- Potential effects of patient diaries on treatment adherence

Limitations to the applicability of individual studies will be identified when these are present. The applicability of the body of evidence for each KQ will be assessed by two reviewers with agreement reached through discussion and consensus when necessary.

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## VI. Definition of Terms

### *Symptom severity*

ARIA guidelines provide the following definitions:<sup>6</sup>

- Mild SAR: lack of sleep disturbance, impairment of daily or leisure activities, impairment of school or work, or troublesome symptoms
- Moderate/severe SAR is characterized by one or more of these disturbances.

The following symptom rating scale is commonly used in SAR clinical trials:<sup>45</sup>

0 = absent symptoms (no sign/symptom evident)

1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)

2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)

3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

### *GRADE*

The Grading of Recommendations Assessment, Development, and Evaluation system assesses the strength of a body of evidence using the following terms:

- 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 effect and may change the estimate.
- Low: low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: evidence either is unavailable or does not permit a conclusion.

## VII. Summary of Protocol Amendments

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In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

## 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

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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 three 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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## Appendix A

### MEDLINE search

1. Rhinitis, Allergic, Perennial/
2. Rhinitis, Allergic, Seasonal/
3. Rhinitis/
4. (seasonal or allergic).tw.
5. 3 and 4
6. seasonal rhinitis.tw.
7. allergic rhinitis.tw.
8. (hay fever or hayfever).tw.
9. (sar or par).tw.
10. or/1-2,5-9
11. exp Adrenal Cortex Hormones/ or corticosteroid\$.tw.
12. Betamethasone/ or (Betamethasone or Celestone).tw.
13. Cortisone/ or Cortone.tw.
14. exp Dexamethasone/ or (Dexamethasone or Baycadron or Hexadrol or Decadron or Dexium or Dexone or DexPak).tw.
15. exp Hydrocortisone/ or (Hydrocortisone or Cortef or Hydrocortone).tw.
16. Methylprednisolone/ or (Methylprednisolone or medrol).tw.
17. exp Prednisolone/ or (Prednisolone or asmaPred Plus or Millipred or Pediapred or Prelone or Veripred or Flo-Pred or Cotelone or Orapred or Prednoral).tw.
18. Prednisone/ or (Prednisone or Liquid Pred or Deltasone or Meticorten or Orasone or Prednicen or Sterapred or Prednicot).tw.
19. exp Triamcinolone/ or (Triamcinolone or Aristocort).tw.
20. or/11-17
21. exp Administration, Oral/ or oral\$.tw.
22. 20 and 21
23. Beclomethasone/ or (Beclomethasone or Beconase or Vancenase).tw.
24. exp Adrenal Cortex Hormones/ or corticosteroid\$.tw.
25. Budesonide/ or (Budesonide or Rhinocort).tw.
26. Pregnenediones/ or (Ciclesonide or Omnaris).tw.
27. exp Dexamethasone/ or (Dexamethasone or Dexacort).tw.
28. exp Fluocinolone Acetonide/ or (Flunisolide or Nasalide or Nasarel).tw.
29. exp Androstadienes/ or (Fluticasone or Flonase or Veramyst).tw.
30. (Mometasone or Nasonex).tw.
31. exp Triamcinolone/ or (Triamcinolone or AllerNaze or Nasocort or Tri-nasal).tw.
32. or/23-31
33. Administration, Intranasal/ or (nasal\$ or intranasal\$.tw.
34. 32 and 33
35. exp Histamine Antagonists/ or antihistamine\$.tw.
36. Cetirizine/ or (Cetirizine or Zyrtec or Alleroff or Aller-tec).tw.

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37. Loratadine/ or (Loratadine or Desloratadine or Clarinex or Claritin or Triaminic or Agistam or Alavert or Bactimicina allergy or Clear-atadine or Loradamed).tw.
38. Terfenadine/ or (Fexofenadine or Allegra).tw.
39. (Levocetirizine or Xyzal).tw.
40. or/36-39
41. exp Histamine Antagonists/ or antihistamine\$.tw.
42. exp Brompheniramine/ or (Brompheniramine or Lodrane or Tridane or Bromaphen or Brovex or B-vex or Tanacof or Bidhist or Bromax or Respa or Brompsiro or Dimetane or Siltane or Vazol or Conex or J-Tan).tw.
43. Carbinoxamine.tw.
44. Pyridines/ or (Carbinoxamine or Carboxine or Cordron or Histuss or Palgic or Pediatex or Pediox or Arbinoxa).tw.
45. Chlorpheniramine/ or (Chlorpheniramine or Chlo-Amine or Chlor-Phen or Krafthist or Chlortan or Ed ChlorPed or P-Tann or Allerlief or Chlor-Al Rel or Myci Chlorped or Pediatan or Ahist or Aller-Chlor or Chlor-Mal or Chlor-Phenit or Diabetic Tussin or Ed Chlor Tan or Ridramin or Teldrin or Uni-Cortrom).tw.
46. Clemastine/ or (Clemastine or Tavist or Allerhist\$ or Dayhist\$).tw.
47. Cyproheptadine/ or (Cyproheptadine or Periactin).tw.
48. (Dexchlorpheniramine or Polaramine).tw.
49. exp Diphenhydramine/ or (Diphenhydramine or Benadryl or Dytan or Kids-eeze or Allergia\$ or Benekraft or Diphenyl or Aler-Dryl or Altaryl or Antihist or Antituss or Beldin or Belix or Bromanate AF or Bydramine or Diphen or Diphenadryl or Diphenyl\$ or Dytuss or Elixsure or Hydramine or Nu-med or Pardyl or PediaCare or Scot-Tussin or Syladryl or Silaphen or Tusstat or Theraflu or Ben Tann or Dicopanor or Allermax or Banophen or Diphedryl or Diphenhist or Nervine or Paxidorm).tw.
50. Doxylamine/ or (Doxylamine or Aldex or Doxytex).tw.
51. Promethazine/ or (Promethazine or Phenergan or Pentazine or Promacot).tw.
52. Tripolidine/ or (Tripolidine or Tripohist or Zymine).tw.
53. exp Dibenzoxepins/ or (Olopatadine or Patanase).tw.
54. exp Phthalazines/ or (Azelastine or Astelin or Astepro).tw.
55. or/41-54
56. Ipratropium/ or (Ipratropium or Atrovent).tw.
57. Cromolyn Sodium/ or (cromoglycate or Cromolyn or Nasalcrom).tw.
58. Leukotriene Antagonists/ or (Leukotriene Antagonist\$ or Montelukast or Singulair).tw.
59. exp Nasal Decongestants/ or exp Phenylephrine/ or Imidazoles/ or (nasal decongestant\$ or Levmetamfetamine or vapo?r inhaler\$ or Naphazoline or Privine or Oxymetazoline or Afrin or (Allerest adj3 Nasal) or Dristan or Duramist plus or Four-Way or Mucinex Nasal or Nasin or Neo-Synephrine or Nostrilla or (NTZ adj3 Nasal) or Oxyfrin or Oxymeta or Sinarest or Zicam or Phenylephrine or Tetrahydrozoline or tyzine or (Alconefrin adj2 Decongestant) or Rhinall or 4-way or Sinex or Propylhexedrine or Benzedrex or Xylometazoline or Otrivin).tw.
60. (oral decongestant\$ or Ah-chew\$ or Gilchew or Phenyl-T or Despec or Lusonal).tw. or exp Pseudoephedrine/ or (Pseudoephedrine or Afrinol or Contac or Efidac or Suphedrine or Decofed or Elixsure or Ephed 60 or Kid Kare or Myfedrine or Q-Fed or Silfedrine or Superfed or Unified or Entex or Nasofed or Congest Aid or Sudophed or Cenafed or Congestaclear or Pseudocot or

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Pseudofed or Pseudotabs or Pseudoval or Ridafed or Seudotabs or Sudafed or Sudodrin or Sudogest or Sudrine).tw.

61. sodium chloride/ or (saline or Altamist or ENTsol or Little Noses or nasal Moist or Ocean or Pretz or Salinex or SaltAire or Deep Sea or Humist or Marine mist or sea Mist or Nasosol or Pediamist or Rhinaris or Sea Soft).tw.

62. (Accuhist or Actacin or Actagen or Actamine or Actedril or Acticon or Actifed or Alacol or Ala-Hist or Alenaze-D or Allan Tannate or Allent or Aller-Chlor or Allercon or AllerDur or Allertest or Allerfrim or Allerx or Altafed or Amerifed or Anamine or Anaplex or Andec or Andehist or Aphedrid or A-Phedrin or Aridex-D or Atridine or Atrogen or Atrohist or Benylin or B-Fedrine or Bi-Tann or BP Allergy or BPM Pseudo or Brexin or Brofed or Brom Tann or Bromadrine or Bromaline or Bromaphedrine or Bromaxefed or BROMDEC or Bromfed or Bromfenex or Bromhist\$ or BROMPHEN or C Tan D or Carbaxefed or CARBIC or Carbiset or Carbodec or Carbofed or Cardec or Centergy or Cetiri-d or Chemdec or Chlor Trimeton or Chlorafed\$ or Chlordrine or Chlor-Mes or Chlorphedrin or Clorfed or Codimal\$ or Coldec or Colfed\$ or Cophene or CP Oral or CP Tannic or C-Phed Tannate or Curaler or Cydec or Dallery or D-Amine or Dayquil Allergy or Deconamine or Decongestamine or De-Congestine or Deconomed or Delsym or Desihist or Dexaphen or Dexophed or Dicel or Dimetapp or Diphentann or Disobrom or Disophrol or Dixaphedrine or Drexophed or Drixomed or Drixoral or D-Tann or Duomine or Duotan or Dura Ron or Durafed or Duralex or Dura-Tap or Duratuss or Dynahist or Ed A-Hist or Endafed or Entre-B or Ex?Dec or Fedahist or Hayfebrol or Hexafed or Hisdec or Histadec or Histafed or Histalet or HistamaxD or Histatab or Hista-Tabs or Histex or Hydro-Tussin or Iofed or Isophen-DF or Klerist-D or Kronofed-A or Lohist or Lortuss or Maldec or Maxichlor or Med-Hist or M-Hist or Mintex or Mooredec or NalDex or Nalfed or Nasohist or ND Clear or NeutraHist or Nohist or Norel LA or Novafed or Novahistine Elixir or Ny-Tannic or Orlenta or Pediachlor or Pharmadrine or Phenabid or PHENAMETH or PHEN-TUSS or Phenyl Chlor Tan or Phenylhistine or Prohist or PSE-BM or Pseubrom or Pseuclor or QDall or Q-Tapp or R?Tann\$ or Relera or Rescon or Respahist or Rhinabid or RhinaHist or Ricobid or Ridifed or Rinade\$ or Rinate or Robitussin Night\$ or Rondamine or Rondec or Rondex or Rymed or Ryna Liquid or Rynatan or Semprex or Seradex or Shellcap or Sildec or Sinuhist or Sonahist or Suclor or SudaHist or Sudal or Sudo Chlor or Suphenamine or SuTan or Tanabid or Tanafed or Tanahist or Tekral or Time-Hist or Touro or TriaFed or Triphed or Tri-Pseudo or Triptifed or Trisofed or Tri-Sudo or Trisudrine or Trynate or Ultrabrom or Vazobid or Vazotab or V-Hist or Vi-Sudo or X-Hist or XiraHist or Zinx Chlor\$ or Zotex).tw.

63. or/22,34,55,62

64. 10 and 63

65. randomized controlled trial.pt.

66. random\$.tw.

67. 65 or 66

68. 64 and 67

69. (animals not humans).sh.

70. 68 not 69

71. limit 70 to english language

72. ("review" or "review academic" or "review tutorial").pt.

73. (medline or medlars or embase or pubmed).tw,sh.

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74. (scisearch or psychinfo or psycinfo).tw,sh.
75. (psychlit or psyclit).tw,sh.
76. cinahl.tw,sh.
77. ((hand adj2 search\$) or (manual\$ adj2 search\$)).tw,sh.
78. (electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.
79. (pooling or pooled or mantel haenszel).tw,sh.
80. (retraction of publication or retracted publication).pt.
81. (peto or dersimonian or der simonian or fixed effect).tw,sh.
82. or/73-81
83. 72 and 82
84. meta-analysis.pt.
85. meta-analysis.sh.
86. (meta-analys\$ or meta analys\$ or metaanalys\$).tw,sh.
87. (systematic\$ adj5 review\$).tw,sh.
88. (systematic\$ adj5 overview\$).tw,sh.
89. (quantitativ\$ adj5 review\$).tw,sh.
90. (quantitativ\$ adj5 overview\$).tw,sh.
91. (quantitativ\$ adj5 synthesis\$).tw,sh.
92. (methodologic\$ adj5 review\$).tw,sh.
93. (methodologic\$ adj5 overview\$).tw,sh.
94. (integrative research review\$ or research integration).tw.
95. or/84-94
96. 64 and 95
97. (animals not humans).sh.
98. 96 not 97
99. limit 98 to english language
100. placebo-controlled.tw.
101. (placebo and (control or controlled)).tw.
102. (observational or cohort or case-control or cross-sectional).tw.
103. or/100-102
104. 64 and 103
105. (animals not humans).sh.
106. 104 not 105
107. limit 106 to english language

## Appendix B

### USPSTF criteria for randomized controlled trials

Good: Meets all criteria outlined below.

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**Fair:** Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential covariates are accounted for. Intention to treat analysis is performed.

**Poor:** Studies will be graded “poor” if any of the following flaws exists: groups assembled initially are not close to being comparable or maintained throughout the trial; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key covariates are given little or no attention. Intention to treat analysis is lacking.

### Criteria

- Initial assembly of comparable groups:
  - For RCTs: potential covariates appropriately distributed
  - For cohort studies: potential confounders controlled
- Maintenance of comparable groups  $\approx < 20\%$  loss to follow-up in each arm
- Measurements equal, reliable, and valid
- Interventions comparable and clearly defined
- All important outcomes considered
- Analysis:
  - For RCTs: intention-to-treat, covariate adjustment
  - For cohort studies: adjustment for potential confounders for cohort studies
- Other aspects of analyses appropriate (e.g. missing data, sensitivity analyses)

## Appendix C

### Deeks criteria for nonrandomized comparative studies

- Was sample definition and selection prospective or retrospective?
- Were inclusion/exclusion criteria clearly described?
- Were participants selected to be representative?
- Was there an attempt to balance groups by design?
- Were baseline prognostic characteristics clearly described and groups shown to be comparable?
- Were interventions clearly specified?
- Were participants in treatment groups recruited within the same time period?
- Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
- Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
- Were outcome measures clearly valid, reliable, and equally applied to treatment groups?

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- Were outcome assessors blinded?
- Was the length of followup adequate?
- Was attrition below an overall high level (<20%)?
- Was the difference in attrition between treatment groups below a high level (<15%)?
- Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

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