ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comparative safety and effectiveness of inhaled corticosteroids and beta-agonists for chronic asthma: Protocol for a systematic review and network meta-analysis

Systematic Review Unit

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Background

Asthma is an inflammatory disorder associated with airway hyper-responsiveness and remodelling (1). It is a common chronic disorder and it is currently estimated to affect 300 million people worldwide with an increasing prevalence in both children and adults. Asthma can lead to substantial healthcare utilization and high economic costs. This economic burden includes direct costs associated with hospitalization and medication use, as well as indirect costs, in the form of loss of work during exacerbation and loss of potential earnings due to morbidity and mortality (2).

According to the *Guidelines for the diagnosis and Management of Asthma* published by the National Asthma Education Program (NAEP) Expert Panel, asthma treatments require continuous control of the symptoms to prevent exacerbations as well as reduce airway inflammation (3). Currently the most effective and widely used treatments for asthma are inhaled corticosteroids (ICS) and inhaled long-acting β_2-agonists (LABA). Combination therapy including both ICS and LABA has been demonstrated to be most effective in treating patients with persistent asthma (4).

There are at least 8 Cochrane reviews that have examined ICS and LABA for chronic asthma. These include the following:
1) Combination budesonide (ICS) and formoterol (LABA) versus β_2-agonists such as terbutaline, salbutamol or formoterol alone for chronic asthma. In this review, 3 randomized clinical trials (RCTs) were included with 5905 children and adults after searching the literature until April 2009. The authors found that there was no clinical advantage for combined budesonide and formoterol as a reliever when compared to formoterol alone in patients with mild chronic asthma. For patients with severe chronic asthma, exacerbation results show that few hospital admissions were reported. Significantly fewer serious adverse events were reported in children using combination of formoterol and budesonide compared to terbutaline alone. However, serious adverse events were not significantly different for combined budesonide versus formoterol in adults. As well, no significant difference was observed for annual growth in children using formoterol and budesonide compared to terbutaline alone (5).
2) Combination budesonide (ICS) and formoterol (LABA) versus current best practice for chronic asthma. In this review, 14 RCTs were included after searching the literature until February 2013. These studies included 13152 adults and adolescent and 224 children participants. The authors found that there was no significant advantage for budesonide (ICS) and formoterol (LABA) in a single inhaler in admission to the hospital compared to both best practice. However, a significant reduction in exacerbations requiring oral steroids was shown for patients treated with budesonide (ICS) and formoterol (LABA) in a single inhaler versus control. Withdrawals due to adverse events were significantly greater in patients receiving budesonide (ICS) and formoterol (LABA) in a single inhaler versus control. In addition, higher dose budesonide maintenance (ICS) and terbutaline reliever was not significantly different than higher dose ICS for hospital admissions. However, patients receiving budesonide maintenance (ICS) and terbutaline reliever were less likely to require oral steroids than those taking ICS. Withdrawals due to adverse events were significantly greater in patients receiving budesonide maintenance (ICS) and terbutaline reliever versus ICS (6).
3) Combination budesonide (ICS) and formoterol (LABA) in a single inhaler as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma. After searching until November 2013, 4 RCTs were included involving 9130 patients over the age of 12 years. Fewer exacerbations requiring oral steroids, admissions to hospital, and ER visits were reported in patients taking combination budesonide (ICS) and formoterol (LABA) in a single inhaler compared with higher fixed-dose combination inhalers (7).
4) Combination fluticasone (ICS) and salmeterol (LABA) versus fixed dose combination budesonide (ICS) and formoterol (LABA) for chronic asthma. Five RCTs and 5537 adults and adolescents were included after

searching the literature until June 2011. No statistically significant results were observed for exacerbations requiring oral steroids, hospital admissions, or serious adverse events (8).
5) Combination ICS and formoterol (LABA) versus regular treatment with salmeterol and ICS for chronic asthma. After searching the literature until August 2011, 10 RCTs with 6769 adults and adolescents were included. No statistically significant results were observed between combination ICS and formoterol (LABA) versus regular treatment with salmeterol and ICS for all-cause non-fatal serious adverse events or asthma-related serious adverse events (9).
6) Combination inhaled corticosteroid (ICS) and salmeterol (LABA) versus the same dose of inhaled corticosteroid (ICS) alone for chronic asthma. Forty RCTs were included with 13447 adults and adolescents and 1862 children. The literature was searched until August 2012. No statistically significant differences were observed between combination inhaled corticosteroid (ICS) and salmeterol (LABA) versus the same dose of inhaled corticosteroid (ICS) alone for mortality, non-fatal serious adverse events, and asthma-related adverse events (10).
7) Combination inhaled corticosteroid (ICS) and formoterol (LABA) versus the same dose of inhaled corticosteroid (ICS) alone for chronic asthma. After searching the literature until August 2012, 27 RCTs including 10578 adults and adolescents and 2788 children and adolescents were included. No differences were observed amongst participants taking formoterol and ICS versus ICS alone for mortality and non-fatal serious adverse events. Adults experienced significantly fewer serious adverse events when administered formoterol and ICS versus ICS alone. However, this was not statistically significant for children (11).
8) Addition to inhaled corticosteroids (ICS) of long-acting β_2-agonists (LABA) versus anti-leukotrienes (LTRA) for chronic asthma. Eighteen RCTs including 7208 adults or children were included after searching the literature until December 2012. Patients receiving ICS+LABA experienced significantly fewer exacerbations requiring oral steroids, improved lung function, increased patient satisfaction, greater quality of life, and required less rescue medication versus those receiving ICS+LTRA. However, patients receiving ICS+LTRA experienced less exercise-induced bronchospasm versus ICS+LABA. No statistically significant differences were observed between ICS+LABA versus ICS+LTRA in overall adverse events, serious adverse events, headache, cardiovascular events, osteopenia and osteoporosis (12).

In addition to these Cochrane reviews, there have been 2 other systematic reviews examining inhalers for chronic asthma. Loymans and colleagues conducted a systematic review and network meta-analysis examining all available asthma maintenance treatments of at least 24 weeks. The authors included a total of 59622 adults from 64 RCTs, and the literature was searched until August 2013. RCTs were included only if the average age of all participants was greater than 18 years. The authors found that combined ICS and LABA treatments were most effective and safe in preventing severe exacerbations of asthma (13). In a second review by Van der Mark and colleagues, children aged 5 to 18 years treated using the recommendations from steps 3 and 4 of with the Global Initiative for Asthma (GINA) guidelines were examined. Authors included 23 RCTs in 4129 children after searching the literature until February 2010. Forty-one studies were excluded because they included a mixture of children and adult participants without reporting the results for adults and children separately. The authors initially wanted to conduct a network meta-analysis, but were not able to because of variation in outcome measurement and reporting (14).

Although many reviews exist on this topic, the 2 previous network meta-analyses did not include children aged 12 years or greater. In order to examine this further, we are proposing to update the Loymans and colleagues network meta-analysis by including RCTs with children aged 12 years or greater (13).

Objective

To examine the comparative safety and efficacy of long-acting inhaled agents (ICS, and LABA) for patients with chronic asthma aged 12 years and greater.

Study Questions:

1) What is the comparative safety and efficacy of inhaled ICSs (alone or in combination) versus inhaled LABA and placebo [in any combination] for patients with chronic asthma aged 12 years and greater?

2) Which intervention (or combination) is the most effective and safe for patients with chronic asthma aged 12 years and greater?

PICO Statement

The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest, is as follows.

Study Population:
Adolescents (≥12 years of age) and adults with asthma. We will report the way that asthma was diagnosed across the included RCTs and conduct a sub-group analysis on this (please see the synthesis section below for further details). We will also consider sub-group analysis by severity of asthma, gender, and age (e.g., 12-18 years of age, ≥65 years of age).

Intervention:
Inclusion: inhaled ICS and LABA (e.g., fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol, and fluticasone and vilanterol). We will focus our analysis on dosage/devices approved for use in Canada. We will also conduct a sub-group analysis on the dosage of ICS, if possible (e.g., low, medium, high).

Exclusion: LAMA (e.g., aclidinium bromide, glycopyrronium bromide, tiotropium, other LAMAs), LABA (nebulizer and transdermal, e.g., arformoterol, tulobuterol, bambuterol), ICS (nebulizer), short-acting $beta_2$-agonists (all agents - oral, inhaler, nebulizer, injection), short-acting anticholinergics (all agents - inhaler and nebulizer), combination short-acting beta-agonist plus anticholinergic in one inhaler (all agents - inhaler and nebulizer), methylxanthines, systemic corticosteroids (oral), and phosphodiesterase-4 inhibitors (oral)

Comparator Groups:
Eligible comparators are: ICS, ICS+SABA, ICS+LABA, ICS+LTRA, LTRA, SABA in any combination and placebo. Concomitant asthma medications will be included if both groups receive the same interventions.

Outcome(s) of Interest:
Potential efficacy outcomes:

1. Symptoms – daytime symptoms (frequency per week, and number of days per week), nighttime symptoms, rescue bronchodilator use, work or school absenteeism, limitation in physical activity
2. Symptom scores - 30 second asthma control test, Juniper's Asthma Control Questionnaire, Asthma Control Test, Asthma Control Scoring System, Pediatric/Adolescent Asthma Therapy Assessment Questionnaire
3. Forced expiratory volume (FEV), peak expiratory flow

4. Exacerbation – overall, resulting in ED visits/hospitalization/unscheduled doctor visit, requiring the use of steroids,
5. Growth (children only)
6. Measures of inflammation – eosinophilia, serum eosinophil cationic protein and sputum eosinophils
7. Quality of life - Asthma Quality of Life Questionnaire, mini- Quality of Life Questionnaire
8. Mortality – overall, asthma-related, respiratory-related, cardiovascular-related
9. Severity – Methacholine challenge test

Potential safety outcomes:

10. Adverse events
11. Serious adverse events
12. Withdrawals – overall, treatment-related

Notes: this list may be truncated if we identify many studies for inclusion, as this is a rapid review.
We will not perform a meta-analysis (or network meta-analysis) on all of these outcomes and will work with all stakeholders to select the two most important efficacy outcomes and safety outcomes with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered (definition of outcomes, use of rescue medication, patient population, disease severity) because this analysis only is valid when homogenous studies, and patient population are included.

Included study designs:
Included: Parallel RCTs
Excluded: Cross-over RCTs

Duration: Studies with at least 24 weeks of treatment will be included.
Other: We will limit inclusion to RCTs written in English. Studies will be excluded if they are animal studies or if there is no quantitative data to abstract (e.g. letters, commentaries).

Methods

The figure in Appendix 1 displays the general approach that we use at the Li Ka Shing Knowledge Institute of St. Michael's Hospital to conduct a systematic review.

Protocol development

The Preferred Reporting Items for Systematic reviews and Meta-analysis for Protocols (PRISMA-P) Statement will guide review reporting of our protocol (15). A draft protocol will be circulated to receive feedback from key stakeholders including the OPDRN, clinicians pharmacoepidemiologists, and systematic review methodologists.

Eligibility criteria

We use the Patients, Interventions, Comparators, Outcomes, Study designs and Time period (PICOST) framework (see above). The draft eligibility criteria can be found in Appendix 2.

Information sources and literature search

To identify RCTs, we will assess all included and excluded studies identified in the 8 Cochrane reviews mentioned above. We will further scan the reference list of the reviews carried out by Loymans (13) and van der Mark (14), as well as collaborate with the authors (Loymans and van der Mark) in conducting this review.

In order to identify unpublished and difficult to locate material (also called grey literature), we will search conference abstracts, trial registries (e.g., www.clinicaltrials.gov), and websites of manufacturers of the inhaled long-acting agents. We will contact authors of conference abstracts, trial protocols, and trial registries to determine whether the RCT has been published in full. If the RCT has not been published, we will request further information on the RCT methods to determine eligibility, as required. Unpublished data from conference abstracts fulfilling our eligibility criteria will be included only if the full publication or conference presentation is unobtainable. Literature saturation will be ensured by searching the reference lists of included studies and reference lists of relevant reviews.

Study selection process

To ensure reliability, a training exercise will be conducted prior to commencing screening. Using the inclusion and exclusion criteria, 25 titles and abstracts (also called citations) from the previous reviews will be screened by all team members. Inter-rater agreement for study inclusion will be calculated using percent agreement and if it is >90% across the team, we will proceed to the next stage. If poor agreement is found, the inclusion and exclusion criteria will be revised. Screening will only commence when the percent agreement is >90%. Two reviewers will screen citations for inclusion, independently (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

Data items and data abstraction process

We will abstract data on study characteristics (e.g., year of conduct [if not reported, we will use the year of publication], sample size, setting [e.g., hospital, community, multi-center, single center], country of study conduct [if not reported, we will use the country of origin of the first author], duration of treatment, timing of treatment [e.g., during the day or at night], duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, severity of asthma, how asthma was diagnosed), and the definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation], hospitalizations [overall or due to exacerbations], , serious adverse events [e.g., a harm resulting in hospitalization]). Finally, we will abstract the outcome results (e.g. number of patients with exacerbations, number of patients hospitalized) for the longest duration of follow-up only, as this is the most conservative approach recommended by the Cochrane Collaboration (16). The data will be extracted and stored in Excel. The draft data abstraction form can be found in Appendix 3. We will create a “cheat sheet” that will accompany reviewers while they are performing data abstraction. This will allow them to navigate the Excel file and result in greater inter-rater reliability. Furthermore, we will conduct a calibration exercise of the data abstraction form and cheat sheet amongst the team. This will entail the entire team conducting data abstraction on a random sample of 10 articles. Data abstraction will only commence when high agreement is achieved (e.g., only minor disagreements/recording errors noted across the team). The data abstraction form and cheat sheet will be revised, if low agreement is observed.

Since this systematic review is being completed in a short time-frame, only the outcome data will be abstracted in duplicate. Discrepancies will be resolved by discussion or the involvement of a third reviewer. Details relating to the study characteristics and patient characteristics will only be abstracted by one person for the ODPRN report. This will subsequently be conducted in duplicate prior to publication.

We suspect that multiple study publications may report data from the same study group (i.e., companion reports). When this occurs, the report with the most complete follow-up data will be included and used to

abstract data. The other report(s) will provide supplementary data only. We also anticipate that studies may report a variety of time-points and where appropriate we will use subgroup analysis to explore this; if 2 studies from the same cohort of patients are reported, the outcome at the oldest age point will be included. We will contact the study authors for further information when the data are not clearly reported. Finally, we will search for errata and retractions for all of the included studies to ensure that the outcome data used in the analysis are correct.

Risk of bias appraisal process

We will appraise the included RCTs using the Cochrane Risk of Bias Tool (17). This will be conducted by one reviewer for the ODPRN report. This will subsequently be conducted in duplicate prior to publication. Publication bias will be assessed using funnel plots for outcomes that have at least 10 of the same treatment comparisons (18).

Synthesis of included studies

We will first describe our systematic review results, reporting study characteristics, patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Prior to considering meta-analysis, we will assess for statistical, clinical, and methodological heterogeneity. If extensive statistical (e.g., a statistically significant Q statistic [$p<0.1$] for heterogeneity or an I^2 statistic greater than 75% (16)), clinical, or methodological heterogeneity (16) is observed we will conduct meta-regression analysis, if feasible depending on the number of eligible studies. The total number of covariates will be constrained so that it is equal to 1/10 the number of studies (19), due to issues with multiple testing in systematic reviews (16). Meta-regression analysis will explore the influence of a few important factors, such as risk of bias results. Both meta-analysis and meta-regression will be analyzed in the R software (20). The relative risk will be calculated for dichotomous values and the mean difference will be calculated for continuous variables (21). The standardized mean difference will be used to pool studies that use different scales for the same outcomes (e.g., quality of life). We anticipate that some of the included studies will not report all relevant data (e.g., standard deviations or standard errors). To include these studies in our analysis, the missing data will be imputed using the median standard deviations reported across the included RCTs or using those from similar RCTs (22).

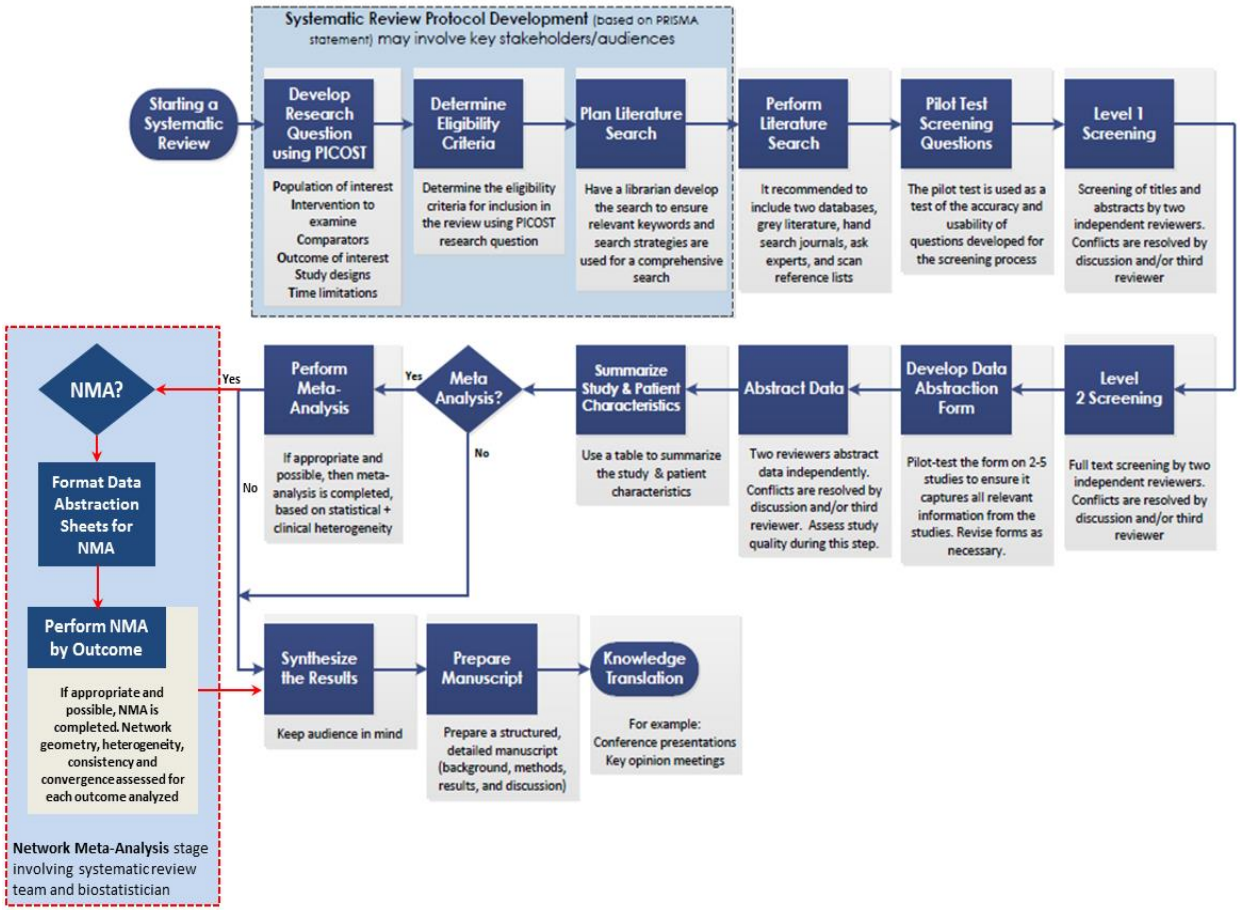
We will explore the effects of subgroups on outcomes to establish the robustness of findings. We will limit the number of subgroup analysis, due to issues with multiple testing in systematic reviews (16). Subgroups that we will explore include the diagnosis of asthma, severity of asthma, age, and definitions of outcomes (exacerbations in particular).

Network meta-analysis will be conducted to derive the combined outcome effect size between each 2 comparisons, as well as rank the safety among all available interventions (23). The placebo group will be used as a reference in the network meta-analysis. To facilitate the practicality of treatment comparisons, median rankings will be used as point estimates of intervention safety. We will use the NODE XL program to present the network meta-analysis results. Network meta-analysis will be conducted in WinBUGS, a Bayesian software program used to build complex statistical models using Markov Chain Monte Carlo simulation.

This will be conducted using a burn-in sample of 50000, followed by 100000 samples for inference. Convergence of the Markov chain Monte Carlo simulation will assessed with the Gelman-Rubin-Brooks plot and diagnostic test (24). Default prior distributions (in all cases non-informative) will be adopted for all parameters in the model. Statistical significance will be expressed by 95% credible intervals that will be established using the 2.5 and 97.5 percentiles obtained via Markov Chain Monte Carlo simulation. We will interpret the 95% credible interval in a similar manner as confidence intervals are interpreted when they are

derived using standard meta-analysis. The consistency of the results between direct versus indirect evidence will be compared using the node-splitting method (25).

Appendix 1: Systematic review process map



Appendix 2: Draft eligibility criteria

Level 1 screening:

1. Does this study include patients aged ≥12 years diagnosed with chronic asthma?
   YES _____
   NO _____
   UNCLEAR _____

2. Is this a randomized clinical trial?
   YES _____
   NO _____
   UNCLEAR _____

3. Does this study examine ANY of the following agents: inhaled ICS and LABA (e.g., fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol, and fluticasone and vilanterol [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

4. Does this study compare a relevant intervention to ANY of the following agents: ICS, ICS+SABA, ICS+LABA, ICS+LTRA, LTRA, SABA in any combination and placebo [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

5. This study likely fulfills our eligibility criteria but is:
   Not written in English _____ (note: will not fully exclude from the review)
   A conference abstract (need to contact authors) _____
   A trial protocol (need to contact authors) _____
   A relevant systematic review (need to scan references) _____

Level 2 screening:

1. Does this study include patients aged ≥12 years diagnosed with chronic asthma?
   YES _____
   NO _____
   UNCLEAR _____

2. Is this a randomized clinical trial?
   YES _____
   NO _____
   UNCLEAR _____

3. Does this study examine ANY of the following agents: inhaled ICS and LABA (e.g., fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol, and fluticasone and vilanterol [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

4. Does this study compare a relevant intervention to ANY of the following agents: ICS,ICS+SABA, ICS+LABA, ICS+LTRA, LTRA,SABA in any combination and placebo [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

5. Does this study report on ANY of the following outcomes that were prioritized by the ODPRN: [once finalized, we will list these outcomes here]
   YES _____
   NO _____
   UNCLEAR _____

6. This study likely fulfills our eligibility criteria but:
   Is not written in English _____ (note: will not fully exclude from the review)
   Is a conference abstract (need to contact authors) _____
   Is a trial protocol (need to contact authors) _____
   Is a relevant systematic review (need to scan references) _____
   Does not contain abstractable data (need to contact authors) _____

➔ If you answer NO to any of these questions, the citation/study will be excluded. All other citations/studies will be included. We will keep track of reviews that have potentially relevant material and will scan their reference lists to ensure all studies have been captured.

Appendix 3: Draft data abstraction form

Study Characteristics

1. First author and year of publication
2. Reference ID number
3. Year of study conduct
4. Sample size
5. Setting (e.g., hospital, community, multi-center, single center)
6. Country of study conduct (if not reported, use the country of origin of the first author)
7. Duration of treatment
8. Total duration of follow-up (includes duration of treatment and subsequent follow-up)
9. Intervention(s) in each arm
10. Comparator (e.g., placebo)

Patient Characteristics

11. Number of patients
12. Mean age and standard deviation (if not reported, the range or interquartile range will be used)
13. Age category (children, children plus adult, adult, elderly [aged 65 years and greater], adult plus elderly)
14. Percent gender
15. Diagnosis of asthma
16. Severity of asthma

Outcome definitions

17. Definition of exacerbations (e.g., at least 1 exacerbation per patient)
18. Definition of hospitalizations (e.g., overall, due to exacerbations)
19. Definition of quality of life (e.g., Asthma Quality of Life Questionnaire, mini- Quality of Life Questionnaire)
20. Definition of serious adverse events (e.g., harm resulting in hospitalization)

Outcome results

[once finalized, we will list all prioritized outcomes here]

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