MIDWEST CEPAC
AN ICER PROGRAM
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

Biologic Therapies for Treatment of Moderate-to-Severe Uncontrolled Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks

Research Protocol

July 19, 2018

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Table of Contents

Background, Objectives, and Research Questions

Background

The Centers for Disease Control and Prevention (CDC) estimates that 20.4 million Americans ages 18 years and older currently have asthma and an additional 6.1 million children have asthma.[1,2] Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging the airways. The disease follows a waxing and waning course with exacerbations initiated by allergens, cold weather, exercise, pollution, and other triggers. This leads to approximately 14.2 million office visits, 1.8 million emergency room visits, and 440,000 hospitalizations each year in the US.[2] The direct medical costs of asthma are estimated to be $50 billion.[2] Individuals with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids and long-acting beta agonist therapy, these patients are often treated with oral corticosteroids.[3]

Among individuals with severe asthma, there are variable clinical presentions and unpredictable responses to therapy. Clinical characteristics have been used to describe different phenotypes of asthma, including phenotypes based on biomarkers of inflammation. About half of individuals with severe asthma have persistent elevation in markers of type 2 inflammation, with elevation in IL-4, 5 and 13 and increased eosinophils in both the blood and airways.[4,5]

This assessment will consider five monoclonal antibodies that alter the pathways involved in the type 2 inflammatory phenotype of asthma. The drugs, dosing, their mechanism of action, and their FDA indications for asthma are summarized in Table 1 below.

Table 1: Monoclonal Antibody Therapies for Moderate-to-Severe Uncontrolled Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate-to-severe persistent asthma who test positive for year-round allergens[6]
Mepolizumab (Nucala®, Glaxo Smith Kline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[7]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[8]
Benralizumab (Fasrena™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[9]
Dupilumab (Dupixent®, Regeneron/Sanofi)	300 mg SC Q 2 weeks	Anti-IL-4Rα	*PDUFA date 10/20/2018[10]

*Dupilumab does not have an FDA indication for asthma at this time.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impact of five biologic therapies for asthma: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan for details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication August 8, 2018).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

- In patients with moderate-to-severe uncontrolled asthma, what is the comparative efficacy, safety, and effectiveness of omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab versus daily inhaled corticosteroids plus at least one additional controller therapy on outcomes such as asthma control, hospitalizations, and quality of life?

- In patients with moderate-to-severe uncontrolled asthma, what is the comparative efficacy, safety, and effectiveness of omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab compared to each other on outcomes such as asthma control, hospitalizations, and quality of life?

PICOTS Criteria

In line with the above research questions, the following criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for the review will be adults and children ages 6 years and older with moderate-to-severe, uncontrolled asthma and evidence of type 2 inflammation and/or allergic asthma. The population is intentionally broad to capture the indicated populations for all of the biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma. Subgroups defined by patient characteristics such as blood eosinophil levels or exacerbation rates in the past year will be reviewed to identify predictors of response and similar patient populations to compare across therapies. Severe asthma is typically defined as asthma that requires either oral corticosteroids for more than 50% of the year or the combination of high-dose inhaled corticosteroids and a long-acting beta-agonist or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[4] We recognize that the definitions of both moderate and severe asthma have evolved over time and differ slightly in the most recent GINA and ERS/ATS guidelines.[4,11] Uncontrolled asthma is typically defined by at least one of the following: frequent exacerbations (2 or more bursts of oral steroid therapy lasting at least 4 days in the past year); at least one serious exacerbation (hospitalization, ICU stay or mechanical ventilation) in the past year; airflow limitation (FEV1 <80% predicted); or poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test < 20).[4] Similarly, we recognize that the definition of an asthma exacerbation varies across the trials. All individuals should be treated with high-dose inhaled corticosteroid therapy and at least one additional controller medication (e.g., long-acting beta-agonists, long-acting muscarinic agents, leukotriene agonists, theophylline, oral corticosteroids).

We will also focus on the subgroup of patients who require long-term oral corticosteroid therapy to maintain control of their asthma.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The interventions of interest will be one of the following added to daily inhaled corticosteroid therapy plus at least one additional controller therapy:

- Omalizumab 75-375 mg by subcutaneous injection once every 2 or 4 weeks

- Mepolizumab 100 mg by subcutaneous injection once every 4 weeks
- Reslizumab 3 mg/kg by intravenous infusion once every 4 weeks
- Benralizumab 30 mg by subcutaneous injection once every 4 weeks x 3; then every 8 weeks
- Dupilumab 300 mg by subcutaneous injection once every 2 weeks

Comparators

The comparators of interest will be daily inhaled corticosteroids plus at least one additional controller therapy, or daily inhaled corticosteroids plus at least one additional controller therapy and one of the other biologics listed. We recognize that there may be insufficient data for direct or indirect comparisons between the five biologic agents that are under review.

Outcomes

This review will examine clinical and health care utilization outcomes related to asthma. Listed below are the outcomes of interest:

- Symptom scale/quality of life including nocturnal symptoms and impact on daily activities (AQLQ)
- Asthma control assessed by standard questionnaires (ACQ or ACT)
- Asthma exacerbations
- Asthma-related hospitalizations and emergency room visits
- Mortality (Asthma-specific and total)
- Use of oral steroids including a reduction in dose for those on chronic oral steroids
- Forced expiratory volume in 1 second (FEV_1)
- Absence from school
- Absence from work
- Adherence

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least 24 weeks duration.

Setting

All relevant settings will be considered, including inpatient, clinic, and outpatient settings, but the focus will be outpatient use of the five therapies.

Study Eligibility Criteria

All eligible randomized controlled trials (RCTs) will be included regardless of sample size as long as they used one of the biologics to be evaluated at the currently recommended dose. Non-

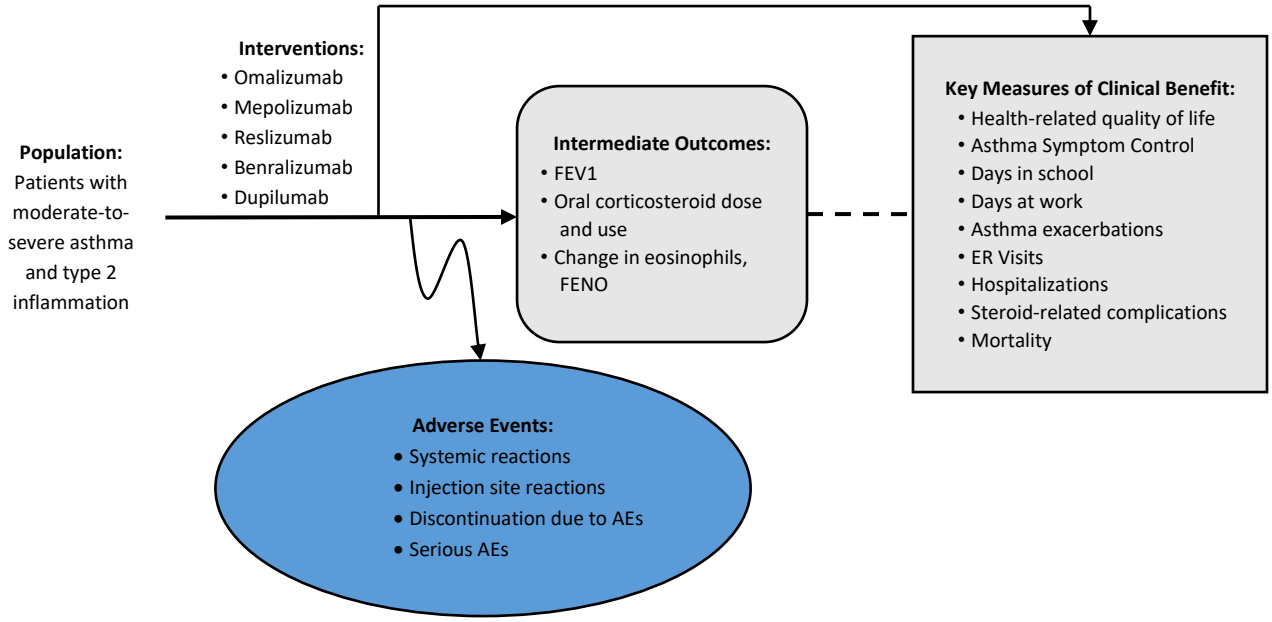
randomized comparative cohort studies and open-label extensions of included RCTs will be included based on criteria that will be finalized after the eligible RCTs have been assessed and the gaps in the evidence base are known.

All eligible studies will be included regardless of publication type or status, including peer-reviewed articles, conference abstracts or presentations, and registry entries (e.g., completed study data from https://clinicaltrials.gov/). In vitro, in silico, animal, and non-English language studies will be excluded.

Analytic Framework

The general analytic framework for assessment of biologic therapies for asthma management is depicted in Figure 1 below.

Figure 1. Analytic Framework: Asthma Management with Biologic Therapies



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., FEV1), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab for moderate-to-severe asthma will follow established best methods.[12,13] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Eligibility criteria described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 2-3 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2: Search Strategy of Medline and Cochrane Central Register of Controlled trials (via Ovid)

1	exp asthma/
2	asthma$.mp.
3	exp bronchial spasm/
4	bronchospas$.mp.
5	(bronch$ adj3 spasm$).mp.
6	exp bronchoconstriction/
7	bronchoconstrict$.mp.
8	(bronch$ adj3 constrict$).mp.
9	bronchial hyperreactivity/
10	respiratory hypersensitivity/
11	((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyper-sensitiv$ or hyperreactiv$ or hyper-reactiv$ or allerg$ or insufficien$ or hyperresponsive$ or hyper-responsive$)).mp.
12	or/1-11
13	omalizumab/

14	omalizumab.ti,ab.
15	(rhuMAB-E25* or Xolair*).ti,ab.
16	mepolizumab.ti,ab.
17	(nucala* or bosatria or sb-240563 or sb240563 or 90Z2UFOE52).ti,ab.
18	(reslizumab or cinqair or cinqaero or cinquil or DCP835 or DCP-835 or CEP38072 or CEP-38072 or SCH55700 or SCH-55700).ti,ab.
19	(benralizumab or fasenra or medi563 or medi-563).ti,ab.
20	(dupilumab or dupixent or regn 668 or regn668 or sar 231893 or sar231893).ti,ab.
21	or/13-20
22	12 and 21
23	(animals not (humans and animals)).sh.
24	22 not 23
25	limit 24 to english language
26	'clinical trial'.ti,ab.
27	'randomized controlled trial'.ti,ab.
28	'randomised controlled trial'.ti,ab.
29	randomi$ation.ti,ab.
30	'single blind'.ti,ab.
31	(double adj2 blind$).ti,ab.
32	placebo.ti,ab.
33	rct.ti,ab.
34	'random allocation'.ti,ab.
35	'randomly allocated'.ti,ab.
36	'allocated randomly'.ti,ab.
37	(allocated adj2 random$).mp.
38	or/26-37
39	((case adj2 study) or (case adj2 studies) or (case adj2 series) or (case adj2 report)).ti,ab.
40	38 not 39
41	40 and 25

Table 3. Search strategy of EMBASE

#1	'asthma'/exp
#2	'asthm*'
#3	'bronchospasm'/exp
#4	'bronchospas*'
#5	bronch* NEAR/3 spasm*
#6	'bronchoconstriction'/exp
#7	bronchoconstrict*
#8	'bronchus hyperreactivity'/exp
#9	'respiratory tract allergy'/exp
#10	(bronch* OR respiratory OR airway$ OR lung$) NEAR/3 (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficien* OR hyperresponsiv)

#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'omalizumab'/exp
#13	'omalizumab':ti,ab
#14	'rhumab e25*':ti,ab OR xolair*:ti,ab
#15	'mepolizumab'/exp
#16	'mepolizumab':ti,ab
#17	nucala*:ti,ab OR bosatria:ti,ab OR sb240563:ti,ab OR 90z2ufoe52:ti,ab
#18	'reslizumab'/exp
#19	reslizumab:ti,ab OR cinqair:ti,ab OR cinqaero:ti,ab OR cinquil:ti,ab OR dcp835:ti,ab OR cep38072:ti,ab OR sch55700:ti,ab
#20	'benralizumab'/exp
#21	benralizumab:ti,ab OR fasenra:ti,ab OR medi563:ti,ab
#22	'dupilumab'/exp
#23	dupilumab:ti,ab OR dupixent:ti,ab OR regn668:ti,ab OR sar231893:ti,ab
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#11 AND #24
#26	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#27	'human'/exp
#28	#26 AND #27
#29	#26 NOT #28
#30	#25 NOT #29
#31	#30 AND [english]/lim
#32	#31 AND [medline]/lim
#33	#31 NOT #32
#34	'clinical trial':ti,ab
#35	'randomized controlled trial'
#36	'randomized controlled trial':ti,ab
#37	'randomised controlled trial':ti,ab
#38	'randomi$ation':ti,ab
#39	'single blind procedure'
#40	(single NEAR/2 blind*):ti,ab
#41	(double NEAR/2 blind*):ti,ab
#42	'double blind procedure'
#43	placebo:ti,ab
#44	rct:ti,ab
#45	(random* NEAR/3 allocat*):ti,ab
#46	random*:ti,ab
#47	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48	((case NEAR/2 stud*):ti,ab) OR ((case NEAR/2 report):ti,ab)
#49	#47 NOT #48
#50	#49 AND #33
#51	#50 AND ('editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#52	#50 NOT #51

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and will work to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

Data extraction will be performed in the following steps:

1. Two reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories “good,” “fair,” or “poor.”[14]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: 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 confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "omalizumab," "mepolizumab," "reslizumab," "benralizumab," and "dupilumab." We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence table shells are presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

If studies are sufficiently similar in terms of patient populations, definition of trial outcomes, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[17] A network meta-

analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)). [18,19] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report. For example, we will look for subgroups, such as those with elevated eosinophils, that would allow for indirect comparisons between drugs. Whether or not formal quantitative comparisons are found to be feasible, descriptive comparisons will be reported.

To explore heterogeneity across studies, we will examine whether there are differences in the distribution of key characteristics across studies. Key characteristics include oral corticosteroid use, exacerbations in the past year, and markers of type 2 inflammation, including sputum and blood eosinophils. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

References

1. Centers for Disease Control and Prevention. National Center For Health Statistics Faststats. 2017; https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed 05/15, 2018.
2. Centers for Disease Control and Prevention. ASTHMA FACTS - CDC's National Asthma Control Program Grantees 2013; https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf. Accessed 05/15, 2018.
3. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of allergy and clinical immunology.* 2007;120(5 Suppl):S94-138.
4. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal.* 2014;43(2):343-373.
5. Barnes PJ. Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. *Nature Reviews Immunology.* 2018.
6. Food and Drug Administration (FDA). Xolair Label. 2007; https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Accessed 05/15, 2018.
7. Food and Drug Administration (FDA). Nucala Label. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed 05/15, 2018.
8. Food and Drug Administration (FDA). Cinquair Label. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed 05/15, 2018.
9. Food and Drug Administration (FDA). Fasenra Label. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed 05/15, 2018.
10. Regeneron. FDA to Review DUPIXENT (dupilumab) as Potential Treatment for Moderate-to-Severe Asthma. 2018; http://files.shareholder.com/downloads/REGN/6263661145x0x973109/0F96ACB7-CB55-494A-B4F9-33E04A49D3B2/REGN_News_2018_3_2_General_Releases.pdf. Accessed 05/15, 2018.
11. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018; https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 06/11, 2018.
12. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
13. Higgins JP, Green S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011].* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.
14. Agency for Healthcare Research and Quality (AHRQ). U.S. Preventive Services Task Force Procedure Manual. 2008; https://www.uspreventiveservicestaskforce.org/Home/GetFile/6/7/procmanual/pdf.

Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[15] Additional explanations of each item can be found in Liberati et al. 2009.[21]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shells

Table B1. Overview of Studies

Reference	Study	Phase	N	FU, weeks	Treatment	Control	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year

Table B2. Quality Metrics

Reference	Study	Adequate Randomization	Allocation Concealment	Patient Blinding	Staff Blinding	Outcome Adjudication Blinding	Completeness of Follow-up	Intention to treat Analysis	Incomplete Data Addressed	Selective Outcome Reporting	Industry Funding	Free from other bias	Overall Quality

Table B3. Outcomes

Reference	Study	Intervention	N	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator	Change in ACG	Change in SGRQ	90-100% reduction in OCS dose	≥50% reduction in OCS dose	No reduction in OCS dose

Table B4. Harms

Reference	Study	Intervention	N	Any AE	SAE	Death	Drug related	Discontinuation due to AEs	Hypersensitivity	Injection reaction	Headache	URI	Sinusitis