Cochrane Library

Cochrane Database of Systematic Reviews

Subcutaneous omalizumab for people with asthma (Protocol)

Donovan T, Milan SJ, Adatia A, Solkar Z, Stovold E, Dwan K, Hinks TSC, Crossingham I

Donovan T, Milan SJ, Adatia A, Solkar Z, Stovold E, Dwan K, Hinks TSC, Crossingham I.
Subcutaneous omalizumab for people with asthma (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD014975.
DOI: 10.1002/14651858.CD014975.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Subcutaneous omalizumab for people with asthma

Tim Donovan[1], Stephen J Milan[2], Adil Adatia[3], Zarina Solkar[4], Elizabeth Stovold[5], Kerry Dwan[6], Timothy SC Hinks[7], Iain Crossingham[8]

[1]Medical Sciences, Institute of Health, University of Cumbria, Lancaster, UK. [2]Health Innovation Campus and Centre for Health Futures, Lancaster University, Lancaster, UK. [3]Department of Medicine, McMaster University, Hamilton, Canada. [4]Lancaster, UK. [5]Cochrane Airways, Population Health Research Institute, St George's, University of London, London, UK. [6]Review Production and Quality Unit, Editorial & Methods Department, Cochrane Central Executive, London, UK. [7]Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK. [8]East Lancashire Hospitals NHS Trust, Blackburn, UK

Contact address: Stephen J Milan, s.milan@lancaster.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 7, 2021.

Citation: Donovan T, Milan SJ, Adatia A, Solkar Z, Stovold E, Dwan K, Hinks TSC, Crossingham I. Subcutaneous omalizumab for people with asthma (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No.: CD014975. DOI: 10.1002/14651858.CD014975.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the effects of subcutaneous omalizumab versus placebo for asthma in adults and children.

BACKGROUND

Description of the condition

Asthma is a respiratory condition affecting the airways. The prevalence of asthma is estimated at 340 million people globally, and is a cause of significant morbidity and mortality. Asthma is characterised by intermittent symptoms of wheeze, dyspnoea, cough, and chest tightness and is physiologically associated with bronchial hyperresponsiveness and variable airflow limitation (Pelaia 2011). Inadequately treated asthma can result in irreversible ventilatory impairment due to fixed airflow obstruction resulting in chronic, persistent symptoms (Perret 2013). The primary treatments for asthma are inhaled corticosteroids and bronchodilators, which are effective for individuals with mild and moderate asthma. However, individuals with severe asthma may require frequent courses or daily oral corticosteroid therapy, a treatment approach that is associated with many adverse effects (Thomson 2012). Individuals with severe asthma have greater hospitalisations and emergency room visits (Hyland 2015), hence the 5% of asthma patients with severe disease account for majority of the economic burden associated with the condition (Antonicelli 2004).

Monoclonal antibody therapies have been developed for optimal treatment of individuals whose asthma is inadequately controlled on inhaled treatments. These novel therapeutics have emerged as a result of an improved understanding of how different pathophysiologic mechanisms, or endotypes, can lead to the various observed asthma phenotypes. All five currently approved biologics for asthma target the type 2 (T2) endotype, which is characterised by increased expression of certain cytokines (interleukin (IL)-4, IL5, and IL13) produced by T-helper 2 CD4 lymphocytes and group 2 innate lymphoid cells (McGregor 2019). Biomarkers used clinically to identify these patients include serum IgE concentration, blood and sputum eosinophils, and fractional exhaled nitric oxide.

Description of the intervention

Immunoglobulin E (IgE) is an essential component in the pathophysiology of allergic asthma (Thomson 2012). In predisposed patients, exposure to an allergen can trigger an immunological cascade culminating in the production of allergen-specific IgE. The IgE antibodies bind to high-affinity IgE receptors (FcεRI receptors) on the cell surface of mast cells and basophils. Subsequent exposure to the allergen is detected by the cell-bound IgE resulting in cross-linking of the IgE molecules and mast cell and basophil degranulation (Spector 1999; Wills-Karp 1999). Cell degranulation releases inflammatory mediators including as histamine, arachidonic acid metabolites (prostaglandins and leukotrienes), and cytokines (IL-3, IL-4, IL-5, and IL-6), with important downstream effects in the airway including bronchoconstriction, eosinophil recruitment, and mucus production (Gauvreau 2015). In a subset of people with asthma, persistent airway inflammation and bronchial hyperresponsiveness may be caused by ongoing allergen-driven activation of these inflammatory pathways owing to elevated serum IgE concentrations (Burrows 1989; Sears 1991).

Omalizumab was initially approved in the United States and Europe in 2003 and 2005, respectively, and is currently indicated for moderate to severe persistent asthma in adults and children six years of age or older with aeroallergen sensitisation and inadequate control with inhaled corticosteroids (McGregor 2019). According to the Global Initiative for Asthma (GINA) report, omalizumab is one of five biologics suggested as an add-on therapy in step 5 after high-dose inhaled corticosteroids and long-acting beta agonists (GINA 2020).

Omalizumab is administered subcutaneously, with the frequency of administration and dose determined by a nomogram relating body weight and total serum IgE concentration. The range of total serum IgE for which omalizumab is indicated varies by age and jurisdiction (United States, age 6 to 11 years 30 to 1300 IU/mL and age ≥ 12 years 30 to 700 IU/mL; European Union, 30 to 1500 IU/mL). However, total serum IgE may not be the optimal biomarker to predict treatment response (Humbert 2014).

How the intervention might work

Omalizumab (also known as Xolair, rhuMAb-E25, or rhu-MAb) is a recombinant humanised IgG1 monoclonal antibody that targets IgE, inhibiting its Fc site binding to the high-affinity receptor FcεRI, found on innate immune cells, particularly on basophils and mast cells. By forming immune complexes with free IgE, interaction between IgE and effector cells is inhibited, with several consequences. Binding free IgE reduces subsequent formation of membrane-bound IgE on mast cells and basophils, reducing the cross-linking that triggers the granulocyte degranulation underlying the early allergic response.

The omalizumab-IgE immune complexes formed are too small to trigger complement activation or to drive immune complex–mediated pathology. Moreover, in contrast to free IgE, when bound to the FcεRI on the cell membrane, the epitope for omalizumab is sterically hindered by the receptor and not accessible, preventing undesirable omalizumab-induced triggering of effector cells.

Omalizumab also reduces surface expression of high-affinity IgE receptors on effector cells including basophils and dendritic cells (Maggi 2018; Thomson 2012), inhibiting their ability to drive naive T cells towards a Th2 phenotype. In addition, omalizumab inhibits IgE binding to the low-affinity IgE receptor on B cells and antigen-presenting cells, and so can induce the absence of an immune response in IgE-bearing B cells (Samitas 2015). Reduction of FcεRI expression on plasmacytoid dendritic cells may enhance antiviral interferon-alpha responses, reducing virus-induced exacerbations (Efthimiou 2019).

Omalizumab accelerates the dissociation of IgE from FcεRI (Eggel 2014), and can reduce serum free IgE, significantly reducing allergen-induced early and late asthmatic responses and improving asthma symptom control (Milgrom 1999).

Why it is important to do this review

Omalizumab is one of a number of monoclonal antibody therapies for asthma to emerge over roughly the last decade. They are recommended in international guidelines as options for individuals with severe asthma (ERS/ATS Guidelines 2020; GINA 2020). Whilst the various monoclonal antibodies do not have identical indications, there is some overlap. Accurate descriptions of the risks and possible benefits of monoclonal therapies such as omalizumab are required to facilitate decision-making by people with asthma and their clinicians as to whether to choose a monoclonal antibody therapy, and to choose between monoclonal therapies.

OBJECTIVES

To evaluate the effects of subcutaneous omalizumab versus placebo for asthma in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported in full text, those published as an abstract only, and unpublished data. We will exclude trials of very short duration (lasting four weeks or less). Because the washout period for this treatment is uncertain, and our primary interest is in exacerbations, we will exclude cross-over studies.

Types of participants

We will include both adults and children (aged six years or older) with a diagnosis of asthma as defined by GINA 2020. We will not exclude participants based on non-respiratory comorbidities, providing they also meet the requirements for a diagnosis of asthma. However, we will exclude those with chronic obstructive pulmonary disease (COPD), as defined by GOLD 2020.

Types of interventions

We will include studies comparing subcutaneous omalizumab with placebo. We will include the following co-interventions, provided they are not part of the randomised treatment: inhaled and oral corticosteroid, inhaled and oral beta agonists, inhaled anticholinergics, xanthines, macrolides, and leukotriene receptor antagonists. We will exclude studies in which participants received other asthma-directed monoclonal antibody therapies (e.g. anti-IL-5 drugs).

Types of outcome measures

We will analyse the following outcomes, but will not use them as a basis for inclusion or exclusion of studies.

Primary outcomes

- Asthma exacerbations as defined by 'events', i.e. hospital admissions, emergency department or urgent care visits, or a need for a course of (or short-term increase in) oral steroid.
- Reduction or termination of steroid (inhaled, oral, or both) use from baseline or run-in period.
- Serious adverse events.

Secondary outcomes

- Measures of asthma control, in the following order of preference: Asthma Control Questionnaire, Asthma Control Test, symptom-free days.
- Health-related quality of life, preferably measured by the Asthma Quality of Life Questionnaire.
- Rescue medication use.
- Measures of lung function, preferably forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF), then other measures.

Search methods for identification of studies

We will conduct database searches and supplementary searches of reference lists to identify reports of relevant studies.

Electronic searches

We will search the following databases and trial registries:

- Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;
- Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date;
- MEDLINE Ovid SP 1946 to date;
- Embase Ovid SP 1974 to date;
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (to be searched via the CENTRAL database).

The proposed MEDLINE search strategy is listed in Appendix 1. The search strategy combines terms for the population and the intervention with the Cochrane Highly Sensitive Search Strategy to identify reports of RCTs (Lefebvre 2021). We will adapt the MEDLINE strategy for use in the other databases. The search strategy was developed by Cochrane Airways Information Specialist Elizabeth Stovold, and peer reviewed by another Cochrane Information Specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan 2016).

We will search all databases and trials registries from their inception to the present, with no restrictions on language or type of publication. We will identify grey literature such as conference abstracts and trial registry records through our searches of the Cochrane Airways Trials Register, CENTRAL, Embase, and ClinicalTrials.gov.

Searching other resources

We will carry out the following supplementary searches:

- identify related systematic reviews and extract their reference lists for screening;
- forwards and backwards citation searches of included studies in the Web of Science platform;
- search pharmaceutical company trial registries and regulatory submissions for additional studies and data;
- search PubMed for errata or retractions from the included studies.

Data collection and analysis

Selection of studies

We plan to use Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

- known assessments: a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT;
- the RCT classifier: a machine learning model that distinguishes RCTs from non-RCTs;

- and, if appropriate, Cochrane Crowd (crowd.cochrane.org), Cochrane's citizen science platform where the Crowd helps to identify and describe health evidence.

More detailed information about the Screen4Me components can be found in the following publications: Marshall 2018, McDonald 2017, Noel-Storr 2018, Thomas 2017.

Following this initial assessment, two review authors (TD, AA) will independently screen the titles and abstracts of the remaining search results, coding them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text reports of all potentially eligible studies, which two review authors (TD, AA) will independently screen for inclusion in the review, and record the reasons for exclusion of ineligible studies. Any disagreements will be resolved through discussion or by consulting a third review author (SJM) if required. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. Two review authors (KD, TD) will extract the following study characteristics from the included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (KD, TD) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data are not reported in a useable way. Any disagreements will be resolved by consensus or by involving a third review author (SJM). One review author (KD) will transfer data into the Review Manager 5 file (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SJM) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SJM, TD) will independently assess risk of bias for each included study using version 2 of the Cochrane risk of bias tool for randomised trials (RoB 2) outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Any disagreements will be resolved by discussion or by involving another review author (IC).

We will assess risk of bias for each study outcome specified in the summary of findings table using the following RoB 2 criteria (Higgins 2021).

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We will judge each outcome as being at low risk, some concerns, or high risk according to the RoB 2 algorithm. We will provide a quote from the study report together with a justification for our judgement in the risk of bias table.

We will reach an overall risk of bias judgement for a specific outcome for each study according to the following criteria.

- Low risk of bias: the trial is judged to be at low risk of bias for all domains for this result.
- Some concerns: the trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- High risk of bias: the trial is judged to be at high risk of bias in at least one domain for this result, or the trial is judged to have some concerns for multiple domains in such a way that substantially lowers confidence in the result.

Our effect of interest is the effect of assignment, or intention-to-treat, and we will summarise the risk of bias in traffic lights on the forest plots. If we include cluster-RCTs in the review, we will use the RoB 2 tool for cluster-randomised trials.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any decisions to deviate from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If we combine data from rating scales in a meta-analysis, we will ensure that they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement). If we calculate an SMD, we will then re-express this on a common scale to facilitate ease of interpretation.

We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (e.g. as medians and interquartile ranges for each group).

If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline. If a study reports outcomes at multiple time points, we will use 12 months (or 52 weeks) in preference to other time points, with 3 months (or 12 weeks) as our second choice.

We will use intention-to-treat, or 'full analysis set', analyses where they are reported (i.e. where data have been imputed for

participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if a study reports rate ratios, we will analyse them on this basis. We will meta-analyse data from cluster-RCTs only if the available data have been adjusted (or can be adjusted by using the intracluster correlation coefficient, as described in the *Cochrane Handbook*) to account for the clustering (Higgins 2021).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE assessment of the affected outcomes.

Assessment of heterogeneity

We will visually assess the forest plot and use the Chi^2 statistic to measure statistical heterogeneity amongst the studies in each analysis. We will measure inconsistency using the I^2 statistic, employing the following as a rough guide to interpretation:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will use a random-effects model, and perform a sensitivity analysis with a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

- Adults versus children (those aged 18 years or more versus those under 18 years).
- Asthma severity (using asthma treatments at trial entry as a surrogate for severity and the GINA 2020 definitions of treatment intensity (steps 1 to 5)).

We will limit subgroup analyses to asthma exacerbations.

We will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses.

- Trials at high risk of bias in at least one domain.
- We will compare the results from a fixed-effect model with those from a random-effects model.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table using the following outcomes.

- Asthma exacerbations as defined by 'events', i.e. hospital admissions, emergency room visits, absence from work/school, unscheduled doctor visits, short-term increases in medications such as oral steroid.
- Reduction or termination of steroid (inhaled, oral, or both) use from baseline or run-in period.
- Adverse events.
- Measures of asthma control, in the following order of preference: Asthma Control Questionnaire, Asthma Control Test, symptom-free days.
- Health-related quality of life, preferably measured by the Asthma Quality of Life Questionnaire.
- Rescue medication use.
- Measures of lung function: preferably FEV_1 or PEF, then other measures.

We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), employing GRADEpro GDT software (GRADEpro GDT). We will justify any decisions to downgrade the certainty of the evidence using footnotes, and will make comments to aid the reader's understanding of the review where necessary.

ACKNOWLEDGEMENTS

The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health and Social Care.

The authors and Cochrane Airways' Editorial Team are grateful to the following peer and consumer reviewers for their time and comments: Sandra Moroz (Canada), M Dulce Estevao (Portugal), Cristoforo Incorvaia (Italy), Giovanni Ferrara (Canada), Sabeeh Kamil (India), J Bardelas (USA), Martha Silvia Martinez-Silveira (Brazil), and Jean Bousquet (France).

REFERENCES

Additional references

Antonicelli 2004

Antonicelli L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, et al. Asthma severity and medical resource utilisation. *European Respiratory Journal* 2004;**23**:723–9.

Burrows 1989

Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE and skin test reactivity to allergens. *New England Journal of Medicine* 1989;**320**:271-7.

Cochrane Airways 2019

Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

Efthimiou 2019

Efthimiou J, Poll C, Barnes PJ. Dual mechanism of action of T2 inhibitor therapies in virally induced exacerbations of asthma: evidence for a beneficial counter-regulation. *European Respiratory Journal* 2019;**54**:1802390.

Eggel 2014

Eggel A, Baravalle G, Hobi G, Kim B, Buschor P, Forrer P, et al. Accelerated dissociation of IgE-FcepsilonRI complexes by disruptive inhibitors actively desensitizes allergic effector cells. *Journal of Allergy and Clinical Immunology* 2014;**133**:1709-19 e8.

ERS/ATS Guidelines 2020

Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. European Respiratory Journal 2020;**55**:1900588. [DOI: 10.1183/13993003.00588-2019]

Gauvreau 2015

Gauvreau GM, El-Gammal AI, O'Byrne PM. Allergen-induced airway responses. *European Respiratory Journal* 2015;**46**(3):819-31.

GINA 2020

Global Initiative for Asthma. Global strategy for asthma management and prevention 2020. ginasthma.org/gina-reports/ (accessed 13 April 2019).

GOLD 2020

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2020 report. goldcopd.org/gold-reports/ (accessed prior to 16 February 2021).

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed prior to 8 July 2021. Hamilton (ON): McMaster University (developed by Evidence Prime), 2021. Available at gradepro.org.

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Humbert 2014

Humbert M, Busse W, Hanania NA, Lowe PJ, Canvin J, Erpenbeck VJ, et al. Omalizumab in asthma: an update on recent developments. *Journal of Allergy and Clinical Immunology Practice* 2014;**2**(5):525-36.e1.

Hyland 2015

Hyland ME, Whalley B, Jones RC, Masoli M. A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales. *Quality of Life Research* 2015;**24**:631–9.

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Maggi 2018

Maggi L, Rossettini B, Montaini G, Matucci A, Vultaggio A, Mazzoni A, et al. Omalizumab dampens type 2 inflammation in a group of long-term treated asthma patients and detaches IgE from FcepsilonRI. *European Journal of Immunology* 2018;**48**:2005-14.

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. In: Global Evidence Summit; 2017 September 13-16; Cape Town, South Africa. 2017.

McGowan 2016

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *Journal of Clinical Epidemiology* 2016;**75**:40-6. [DOI: 10.1016/j.jclinepi.2016.01.021]

McGregor 2019

McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *American Journal of Respiratory and Critical Care Medicine* 2019;**199**(4):433-45.

Milgrom 1999

Milgrom H, Fick RB, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *New England Journal of Medicine* 1999;**341**(26):1966-73.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Noel-Storr 2018

Noel-Storr AH, Project Transform team. Cochrane Crowd: new ways of working together to produce health evidence. In: Evidence Live; 2018 June 18-20; Oxford, UK. 2018.

Pelaia 2011

Pelaia G, Gallelli L, Renda T, Romeo P, Busceti MT, Grembiale RD, et al. Update on optimal use of omalizumab in management of asthma. *Journal of Asthma and Allergy* 2011;**4**:49-59.

Perret 2013

Perret JL, Dharmage SC, Matheson MC, Johns DP, Gurrin LC, Burgess JA, et al. The interplay between the effects of lifetime asthma, smoking, and atopy on fixed airflow obstruction in middle age. *American Journal of Respiratory and Critical Care Medicine* 2013;**187**(1):42-8.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Samitas 2015

Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *European Respiratory Review* 2015;**24**:594-601.

Sears 1991

Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relationship between airways responsiveness and serum IgE in children with asthma and in apparently normal children. *New England Journal of Medicine* 1991;**325**:1067-71.

Spector 1999

Spector SL. Allergic inflammation in upper and lower airways. *Annals of Allergy, Asthma & Immunology* 1999;**83**:435-44.

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al. Living systematic review network. Living systematic reviews: 2. Combining human and machine effort. *Journal of Clinical Epidemiology* 2017;**91**:31-7.

Thomson 2012

Thomson NC, Chaudhuri R. Omalizumab: clinical use for the management of asthma. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2012;**6**:27–40.

Wills-Karp 1999

Wills-Karp M. Immunologic basis of antigen-induced airway hyperresponsiveness. *Annual Review of Immunology* 1999;**17**:255-81.

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE(R) ALL <1946 to June 11, 2021>

#	Searches	Results
1	exp Asthma/	132032
2	asthma$.ti,ab.	163352
3	1 or 2	184548
4	Omalizumab/	1856
5	omalizumab$.ti,ab.	2531
6	Xolair.ti,ab.	131
7	rhuMAb-E25.ti,ab.	39
8	rhu-Mab.ti,ab.	5

(Continued)

9	anti-IgE$.ti,ab.	3341
10	"anti-immunoglobulin E".ti,ab.	268
11	or/4-10	5532
12	randomized controlled trial.pt.	533233
13	controlled clinical trial.pt.	94205
14	randomi?ed.ab,ti.	675481
15	placebo.ab,ti.	224701
16	dt.fs.	2328849
17	randomly.ab.	359382
18	trial.ab,ti.	647081
19	groups.ab.	2205980
20	or/12-18	3438877
21	exp animals/ not humans.sh.	4840864
22	20 not 21	3084006
23	3 and 11 and 22	1262

CONTRIBUTIONS OF AUTHORS

Tim Donovan (TD): protocol: Background, Methods section, and References. Planning also to contribute to Results, Summary of findings, Discussion, Authors' conclusions, Abstract, and Plain language summary.

Stephen Milan (SJM): protocol: Background, Methods section, and References. Planning also to contribute to Results, Discussion, Authors' conclusions, Abstract, and Plain language summary.

Adil Adatia (AA): protocol: Background, Methods section, and References. Planning also to contribute to Results, Discussion, Authors' conclusions, Abstract, and Plain language summary.

Zarina Solkar (ZS): protocol: Background and Methods sections. Planning also to contribute to Discussion, Authors' conclusions, and Plain language summary.

Elizabeth Stovold (ES): protocol: Search methods section, search strategy, References. Planning also to conduct the literature searches and contribute to Results, Discussion, Authors' conclusions, Abstract, and Plain language summary.

Kerry Dwan (KD): protocol: Background, Methods section, and References. Planning also to contribute to Results, Discussion, Authors' conclusions, Abstract, and Plain language summary.

Timothy SC Hinks (TSCH): protocol: Background, Methods section, and References. Planning also to contribute to Discussion, Authors' conclusions, and Abstract.

Iain Crossingham (IC): protocol: Background, Methods section, and References. Planning also to contribute to Results, Discussion, Authors' conclusions, and Abstract.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor) edited the protocol; advised on methodology; approved the protocol prior to publication.

Alexander G Mathioudakis (Contact Editor): edited the protocol; advised on content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.

Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the protocol.

Elizabeth Stovold (Information Specialist): designed the search strategy; arranged for peer review of the search strategy.

DECLARATIONS OF INTEREST

Tim Donovan: none

Stephen Milan: none

Adil Adatia: is supported the Canadian Institute for Health Research/Canadian Allergy, Asthma, and Immunology Foundation/AstraZeneca/AllerGen Emerging Researcher Award in Allergic Asthma.

Zarina Solkar: none

Elizabeth Stovold: is funded by the NIHR core grant in Cochrane Airways, and employed by St George's, University of London.

Kerry Dwan: is employed by Cochrane's Editorial and Methods Department.

Timothy SC Hinks: has received research funding from the Wellcome Trust, NIHR, and the Academy of Medical Sciences. He has received speaker fees from AstraZeneca and Boehringer Ingelheim, and his research team has received funding from Sanofi.

Iain Crossingham: works in a clinically relevant speciality (respiratory medicine).

SOURCES OF SUPPORT

Internal sources

- Lancaster University, UK

  Lancaster University provided Steve Milan's salary
- University of Cumbria, UK

  Cumbria University provided Tim Donovan's salary
- St George's, University of London, UK

  St George's, University of London provided Elizabeth Stovold's salary

External sources

- The Wellcome Trust, UK

  Timothy Hinks is supported by a Career Development Fellowship from the Wellcome Trust (211050/Z/18/Z).
- NIHR Oxford BRC, UK

  Timothy Hinks is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).