CICER
Tacaíocht don Treoirlíne Chliniciúil
Clinical Guideline Support

ANTI-INTERLEUKIN-5 THERAPY IN ADULTS PRESENTING TO HOSPITAL WITH ACUTE ASTHMA

Systematic review of clinical and cost-effectiveness

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NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

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About CICER

In 2016, the Department of Health requested that the Health Research Board (HRB) fund an evidence synthesis service to support the activities of the Ministerially appointed National Clinical Effectiveness Committee (NCEC). Following a competitive process, the Health Information and Quality Authority (HIQA) was awarded research funding spanning the period from 2017 to 2024 to produce the evidence to support the development of National Clinical Guidelines. This funding was renewed through a competitive process to support the work of the Centre in Ireland for Clinical guideline support and Evidence Reviews (CICER) from 2024 to 2028. CICER comprises a dedicated multidisciplinary research team supported by staff from the Health Technology Assessment team in HIQA, the Discipline of Public Health and Primary Care in the School of Medicine in Trinity College Dublin, as well as national and international clinical and methodological experts.

With regard to clinical guidelines, the role of the CICER team is to independently review evidence and provide scientific support for the development, (by guideline development groups (GDGs)), of National Clinical Guidelines for the NCEC. The CICER team undertakes systematic reviews of the clinical effectiveness and cost effectiveness of interventions included in the guidelines, as well as estimating the budget impact of implementing the guidelines. The CICER team also works closely with the GDGs and provides tailored training sessions; assists in the development of clinical questions and search strategies; performs systematic reviews of international clinical guidelines and supports the assessment of their suitability for adaptation to Ireland; and supports the development of evidence-based recommendations informed within the National Clinical Guidelines.

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Plain Language Summary

Asthma is a long-term health issue that can impact breathing. People are more likely to develop asthma if they have a family history, allergies, airway infections early in life, and or exposure to tobacco smoke or air pollution. An asthma attack is when a person's asthma symptoms become temporarily worse. Sometimes people have to go to the emergency department or hospital when they are having an asthma attack, and sometimes asthma attacks can be very serious or even fatal.

There are many different medical approaches to treat asthma and asthma attacks. Anti-interleukin-5 medicine, or anti-IL-5 medicine, is a new type of treatment for asthma. Anti-IL-5 medicine is used to help some people living with asthma to remain healthy and reduce or prevent asthma attacks. Anti-IL-5 medicine works best for people whose asthma is caused by high levels of certain white blood cells in the airways of the lungs. This medicine works by blocking a signal that tells those white blood cells to go to the lungs and cause inflammation, which results in asthma symptoms. Some research shows that anti-IL-5 medicine may also be helpful for people while they are having an asthma attack.

The National Clinical Guideline for Management of an Acute Asthma Attack in Adults in Ireland was published in 2015. This guideline is being updated to help healthcare providers and patients make informed decisions about managing asthma attacks. The CICER team has been asked to look at the research on whether anti-IL-5 medicine works to treat acute asthma attacks, as well as the economic impact of using anti-IL-5 medicine for this reason.

To find studies about anti-IL-5 medicine for asthma attacks, we searched databases of scientific studies. We looked for studies that:

- included adults (aged 16 years or over)
- used anti-IL-5 medicine when a person came to hospital to treat an asthma attack
- were published in scientific databases between September 2022 and June 2025
- reported on specific measurements of importance to patients and clinicians, which were agreed with the guideline development group beforehand and grouped by importance.

  - Note: The "critical", or most important, measurements of interest were whether the patient died or was placed on a breathing machine during the original hospital visit, and whether the patient had further severe asthma attacks that needed a hospital visit, in the months after the original hospital visit.
- used a study design that:
  - placed similar people randomly into groups and compared the group that received anti-IL-5 medicine to another group that was treated as usual; or
  - looked at the economic impact of using anti-IL-5 medicine to treat an asthma attack.

We found one small study that looked at whether anti-IL-5 medicine works as a treatment for asthma attacks in a person presenting to the emergency department and or being admitted to hospital. Using an international checklist, we found that this study was well designed and well conducted, and that the results were likely to be reliable. The study did not look at all of the measurements that we were interested in, and for some results, asthma was grouped with other lung diseases. This made it impossible to pull out some results for the group of patients with asthma.

Patients with asthma who received anti-IL-5 medicine had less than half the risk of experiencing another asthma attack up to 90 days after treatment, compared to the group receiving routine treatment alone. The asthma patients who received anti-IL-5 medicine reported better control of their asthma and asthma-related quality of life at 28 days, compared to the group with routine treatment. We did not find any studies that looked at the economic impact of anti-IL-5 medicine for asthma attack.

Even though we searched carefully for studies, we only found one study that looked at how well anti-IL-5 medicine works for treating asthma attacks in hospital. The study showed some positive results, however it was a small study. We found no study that looked at the economic impact of the treatment. To fully understand the benefits and risks of this treatment, more studies are needed on this topic.

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List of abbreviations that appear in this report

ABRA	Acute exacerbations treated with BenRAlizumab
ACQ-7	Asthma Control Questionnaire 7
ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
CICER	Centre in Ireland for Clinical guideline support and Evidence Reviews
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EuroQol	European Quality of Life
FEV1	forced expiratory volume
GDG	guideline development group
HIQA	Health Information and Quality Authority
HRB	Health Research Board
HSE	Health Service Executive
ICER	incremental cost-effectiveness ratio
IL-5	interleukin-5
NCEC	National Clinical Effectiveness Committee
PCRS	Primary Care Reimbursement Service
PEF	peak expiratory flow
PICO	population, intervention, comparison, outcome
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomised controlled trial
RoB	risk of bias
VAS	visual analogue scale

1 Background

1.1 Description of the condition

Asthma is defined as a chronic inflammatory disorder, in which the bronchial airways in the lungs become narrow and swollen, impacting breathing.[1, 2] Asthma can range in severity from mild to severe, with typical symptoms including wheezing, coughing, shortness of breath, and chest tightness.[3] Asthma is a "complex genetic disorder with strong environmental influence", whose risk factors include air pollution, smoking, atopy (a genetic tendency to develop an exaggerated immune response), stress, and obesity.[4, 5] Asthma is associated with an increased risk of accompanying health conditions, including rhinitis, sinusitis, gastroesophageal reflux, and obstructive sleep apnoea.[6, 7] In Ireland, approximately 5-10% of the adult population has been diagnosed with asthma.[8-10] Occasionally, individuals with asthma may experience a sudden worsening of their symptoms, also known as an asthma exacerbation or an asthma attack. Asthma attacks are characterised by rapid breathing, difficulty speaking, accelerated heart rate, and low oxygen saturation and may vary in severity from mild to life-threatening.[11] They can be triggered by viral respiratory infections, like the common cold, or by exposure to allergens.[12, 13]

1.2 Medical management of asthma exacerbations

Medical management of asthma involves a stepwise approach, with a combination of bronchodilator (such as salbutamol, terbutaline, and ipratropium bromide) and steroid (such as fluticasone, beclomethasone, and budesonide) inhalers used, either only as needed or as maintenance therapy. Bronchodilator inhalers can help to relax the lung muscles and open up the air passages to relieve symptoms,[14] while steroid inhalers work by reducing inflammation in the airway. More severe chronic asthma may require management with oral medicines, such as leukotriene receptor antagonists or steroid tablets, or with injectable biologic therapies.[15]

Asthma attacks are typically treated with a combination of inhaled short-acting bronchodilators and systemic corticosteroids.[15] Severe asthma attacks may become life-threatening and require emergency medical intervention. Emergency treatment for an acute asthma attack may include nebulised bronchodilators (such as short-acting beta-2 agonists

and ipratropium bromide), corticosteroids, and supplementary oxygen, and in very severe cases, mechanical ventilation.[16] Experiencing repeated severe asthma attacks can lead to an accumulation of risk for patients, including increased likelihood of further attacks.[17] In 2023, there were 3,495 discharges from inpatient care with a principal diagnosis of asthma in Ireland; 98% (n=3,427) of these were "emergency admissions", meaning that they were unplanned admissions requiring immediate care and treatment and were likely admitted through the emergency department.[18, 19]

1.3 Anti-interleukin-5 therapy in asthma

There are many inflammatory pathways involved in asthma, but eosinophils, a type of white blood cell, plays a critical role in the pathogenesis and severity of the disease.[20] Asthma is associated with tissue eosinophilia (defined as the presence of an excessive amount of eosinophils in the blood) in 40–60% of patients,[21] and the intensity of eosinophilia has been correlated with asthma severity.[22] Interleukin (IL)-5 is the key cytokine (signalling protein) in the maturation, activation, proliferation, migration and survival of eosinophils.[23] Eosinophilic asthma is often therapeutically responsive to corticosteroids, due to the effective ability of corticosteroids to induce apoptosis (cell death) in eosinophils.[24] However, severe eosinophilic asthma may be resistant to both inhaled and systemic corticosteroids, partly because of an excessive bronchial amount of IL-5.[25, 26] IL-5 has therefore become a therapeutic target for eosinophilic asthma. In recent years, two monoclonal antibodies (mepolizumab and reslizumab) directed against IL-5 and one monoclonal antibody directed against the alpha-subunit of the IL-5 receptor (benralizumab) have been developed.[27] Mepolizumab, reslizumab, and benralizumab received initial European Medicines Agency approval between 2015 and 2018 and are currently licensed as an add-on maintenance treatment for patients with severe eosinophilic asthma.[28]

A 2025 systematic review and meta-analysis found that administering anti-IL-5 therapy in severe eosinophilic asthma as an add-on maintenance treatment was associated with a 62% reduction in severe exacerbations and a 54% reduction in hospitalisations at 12 months following treatment initiation (compared to pre-treatment), and a 51% reduction in oral corticosteroid use.[29] In Ireland, this therapy must be initiated by a consultant respiratory physician. It is currently licensed as an add-on maintenance treatment in adult patients with

severe eosinophilic asthma that is inadequately controlled, despite high-dose inhaled corticosteroids plus long-acting β-agonists.[30] Mepolizumab and benralizumab are administered as a subcutaneous injection and are reimbursable through the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS), while reslizumab is administered as an intravenous infusion in a hospital setting only.[30] Neither therapy is licensed for treatment of an acute exacerbation of asthma.

As of September 2025, no clinical guidelines recommend the use of anti-IL-5 therapy for acute asthma exacerbations, and there is limited evidence about its potential role in the management of acute exacerbations and how it may be associated with future exacerbations and other outcomes. Case reports suggest that anti-IL-5 therapy may be beneficial for some patients experiencing severe eosinophilic asthma exacerbations.[31-34] A systematic search of evidence for anti-IL-5 therapy used in the context of acute asthma exacerbations was carried out in 2022 during the development of Dutch asthma management guidelines,[35] with no relevant studies identified.

1.4 Purpose of the review

The purpose of this systematic review was to identify and evaluate the clinical and economic evidence relating to anti-IL-5 therapy for an acute asthma exacerbation in those presenting to the emergency department and or being admitted to hospital. This will help to inform the recommendations of the upcoming update of NCEC National Clinical Guideline on Management of an Acute Asthma Attack in Adults (aged 16 years and older).

2 Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[36] The completed PRISMA statement checklist is available in Appendix 1. National HIQA guidelines were adhered to for identifying and evaluating clinical and economic evidence.[37, 38] The review was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO) database of systematic reviews and meta-analyses (record number: CRD420251105241).[39]

2.1 Review question

This review considered the following research question:

> *What is the clinical and cost-effectiveness of anti-IL-5 therapy for the management of asthma symptoms in adults presenting to hospital with an acute exacerbation of asthma, either as an add-on to or instead of usual treatment?*

This question was formulated in line with the Population, Intervention, Comparison, Outcome (PICO) framework, as presented in Table 2.1. "Critical" and "important" outcomes were identified in collaboration with the patient representatives on the GDG.

Table 2.1 PICO framework for anti-IL-5 therapy for acute exacerbations of asthma

Population	Patients aged 16 years or older with an acute exacerbation of asthma in the acute urgent care setting (emergency department, inpatient, or intensive care unit)
Intervention	**Include:** ▪ Treatment with an anti-IL-5 therapy (including reslizumab, mepolizumab or benralizumab) during an acute exacerbation that requires presentation to emergency department and or hospital admission for treatment. **Exclude:** ▪ Use of anti-IL-5 therapy as an ongoing maintenance treatment.
Comparison	Usual care or other treatment or no treatment
Outcome	**"Critical" outcomes:** ▪ Death during current visit ▪ Intensive care admission during current visit ▪ Ventilation during current visit

	▪ Subsequent severe asthma exacerbations requiring emergency department visit and or inpatient admission within a timeframe of up to 90 days (number of events and or proportion of patients experiencing events) **"Important" outcomes:** ▪ Length of current stay in hospital, if admitted ▪ Adverse events within a timeframe of up to 90 days (for example nasopharyngitis, headache, upper respiratory tract infection, bronchitis, hypersensitivity) (number of events and or proportion of patients experiencing events) ▪ Serious adverse events requiring hospitalisation within a timeframe of up to 90 days (number of events and or proportion of patients experiencing events) ▪ Subsequent asthma exacerbation (any severity, defined as an exacerbation requiring a change in treatment), within a timeframe of up to 90 days (number of events and or proportion of patients experiencing events) ▪ Asthma control (for example Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), within a timeframe of up to 90 days) ▪ Asthma-related quality of life (for example Asthma Quality of Life Questionnaire (AQLQ), EuroQoL 5-Dimension 5-Level (EQ-5D-5L), within a timeframe of up to 90 days) ▪ Any relevant measures of costs and benefits that may be applicable to the Irish setting, see section 2.2.
Study design	**Include:** ▪ Randomised controlled trials ▪ Economic evaluation studies **Exclude:** ▪ Observational studies
Search period	September 2022 – June 2025

2.2 Health economic studies

This systematic review aimed to identify health economic studies including economic evaluations (cost-effectiveness analyses, cost-utility analyses, cost-minimisation analyses

and cost-benefit analyses) related to the review questions. Economic outcome measures considered applicable to this review include:

Economic evaluations

- Cost-utility and or cost-effectiveness analysis:
  - incremental cost-effectiveness ratio
  - cost per unit of effect (such as cost per life year gained) or effects per unit cost (for example, life years gained per Euro spent)
  - quality-adjusted life years, disability-adjusted life years, or health/life years equivalent
  - incremental net monetary benefit.
- Cost-benefit and or cost-minimisation analysis:
  - net monetary benefit
  - incremental costs.

Other economic outcome measures

- Costs and resource use:
  - direct (for example, cost of staffing and equipment) and indirect (for example, lost productivity) costs, offsets and savings
  - implementation costs (for example, training and education)
  - service utilisation cost.

2.3 Search strategy

The search terms were informed by a similar 2022 systematic review of clinical effectiveness of anti-IL-5 therapy for acute asthma exacerbation, conducted for a Dutch national clinical guideline.[35] That previous search was run from inception until 31 August 2022, with no studies meeting the inclusion criteria. The search strategy employed in the 2022 systematic review was quality-appraised using the Peer Review of Electronic Search Strategies (PRESS) tool[40] and adapted and approved for use by CICER's in-house librarian. The current updated search was run from 1 September 2022 until 18 June 2025. Electronic searches were conducted in MEDLINE via Ovid, Embase via Elsevier, Cochrane Library, and ClinicalTrials.gov. The Medline search strategy is included in Appendix 2 and complete

search strategy documentation is available from the open repository zenodo: https://zenodo.org/records/17174835.

In addition to the database search, backward-citation and forward-citation screening was conducted for eligible studies using "citationchaser" software on 11 August 2025.[41] A grey literature search, beyond ClinicalTrials.gov was not conducted, as any relevant randomised controlled trials (RCTs) were expected to be published in peer-reviewed journals and captured by the database search.

2.4 Selection of eligible publications

All citations identified from the collective search strategy were exported to EndNote (Version 20) for reference management, where duplicates were identified and removed. Using Covidence (www.covidence.org), two reviewers independently reviewed the titles and abstracts of the remaining citations to identify those eligible for full-text review. The full texts were obtained and independently evaluated by two reviewers who applied the defined inclusion and exclusion criteria (see Table 2.1). Where disagreements around eligibility occurred, discussions were held to reach consensus and a third reviewer was consulted where necessary. Citations excluded during the full-text review stage were documented as well as the reason for their exclusion and these were included in a PRISMA flow diagram.

2.5 Data extraction and management

Data extraction was conducted independently by two reviewers using an agreed data extraction template and compared for accuracy and omissions. Extracted data included study characteristics (year of publication, country, study design, number of participants, description of the intervention, description of the comparison groups, and outcomes used) and numerical results for the outcomes identified as "Critical" and "Important" for the purpose of this review. Effect measures include hazard ratios (for subsequent exacerbations of any severity) and mean difference (for asthma control and quality of life).

2.6 Quality appraisal

Two reviewers independently assessed the quality of the included studies using Cochrane Risk of Bias (RoB) 2 for RCTs.[42] As only one study was identified for the purpose of the review, with no evidence related to the "critical" outcomes selected, the Grading of Recommendations Assessment, Development, and Evaluation) framework[43] was not used to assess certainty of evidence.

2.7 Data synthesis

A narrative synthesis of the study characteristics, quality appraisal, and evidence related to "critical" and "important" outcomes was conducted.

3 Results

3.1 Search results

The search of electronic databases identified 536 citations. After removal of duplicates, the titles and available summaries of 433 citations were independently screened by two reviewers, after which 432 records were excluded. One full text was sought for retrieval, independently assessed by two reviewers who applied the predefined inclusion and exclusion criteria, and this full-text study included in the review. Backward-citation and forward-citation searching for the included record identified 35 backward-citation and 50 forward-citation results. Following screening of these citations for relevance, one additional record was identified and retrieved. On full-text review, this additional record was found to be ineligible. A PRISMA flow chart summarising the search process and subsequent results is provided in Figure 3.1 PRISMA flow diagram.

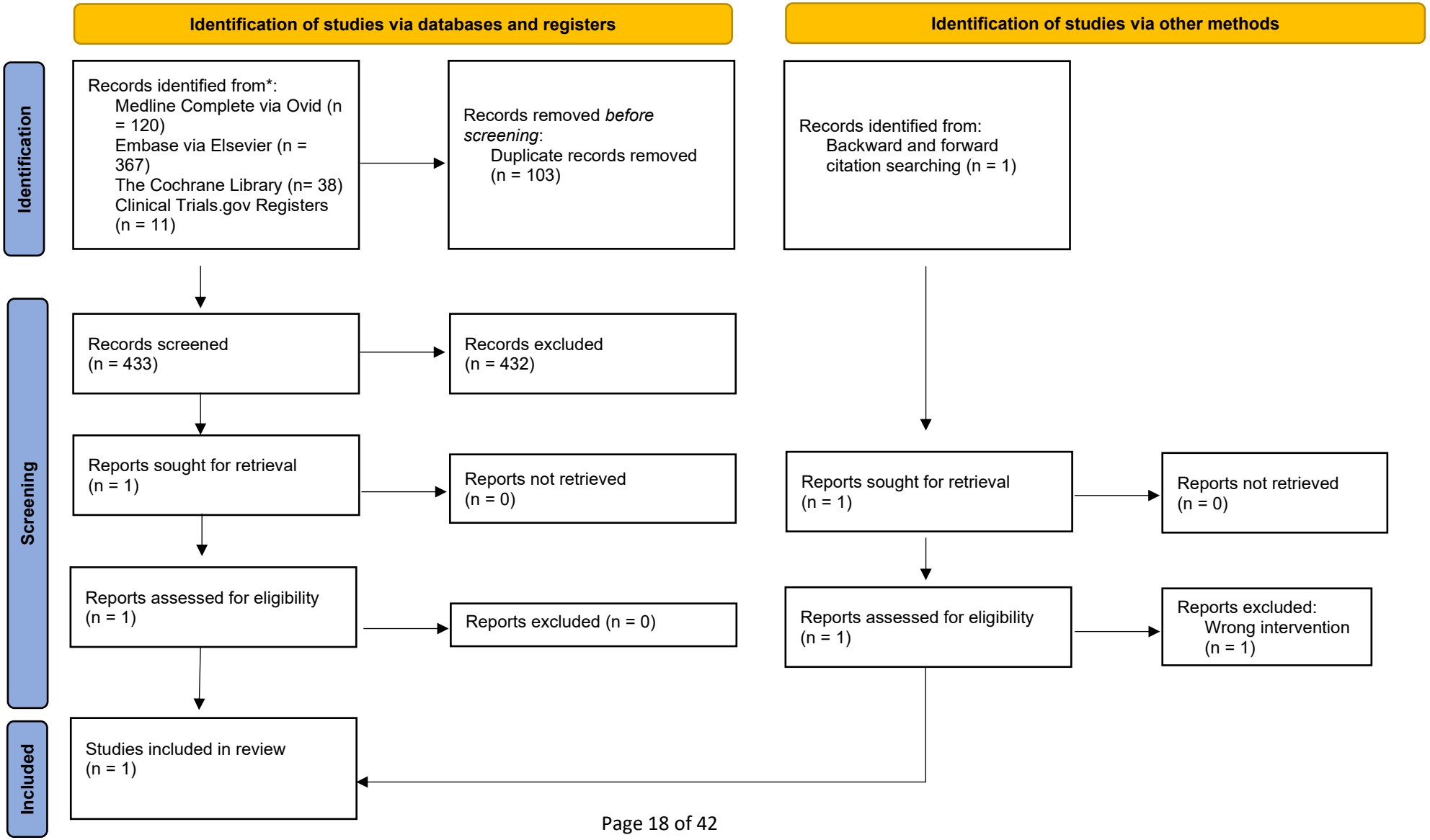
3.2 Study characteristics

One study met the inclusion criteria for the purpose of this review.[44] The Acute exacerbations treated with BenRAlizumab (ABRA) RCT was conducted in the UK and published in 2025. The study included 158 individuals who met the study's inclusion criteria (18 years of age or older, experiencing an acute exacerbation of asthma and/or chronic obstructive pulmonary disease (COPD), and a blood eosinophil count ≥300 cells/microlitre), who were randomised to one of three groups:

- Group 1 (n=53): benralizumab as a single 100 mg subcutaneous injection and oral placebo tablet daily for five days
- Group 2 (n=52): benralizumab as a single 100 mg subcutaneous injection and oral prednisolone 30 mg daily for five days
- Group 3 (n=53): placebo subcutaneous injection and oral prednisolone 30 mg daily for five days.

Eighty-eight (56%) of the included participants were diagnosed with asthma, 51 (32%) with COPD, and 19 (12%) with both asthma and COPD. Eight-six (54%) were female and 72 (46%) were male, and the mean age was 57 years (range, 18-84 years).

Figure 3.1 PRISMA flow diagram



The primary outcomes of interest were:

- rate of treatment failure (defined as a composite of death, admission to hospital, and any need for re-treatment requiring systemic glucocorticoids or antibiotics) within 90 days
- total visual analogue scale (VAS) scores at day 28 for the symptoms of cough, wheeze, dyspnoea, sputum production, and sputum purulence.

Secondary outcomes for asthma patients included:

- treatment failure risk within 30 days of randomisation
- time to treatment failure
- forced expiratory volume (FEV1)
- peak expiratory flow (PEF)
- ACQ-7
- ACT
- AQLQ
- EuroQoL.

3.3 Risk of bias

Two reviewers independently assessed risk of bias in the results of the "critical" and "important" outcomes (as outlined in Table 2.1) using Cochrane's RoB 2 tool, assessing risk of bias according to the following domains:

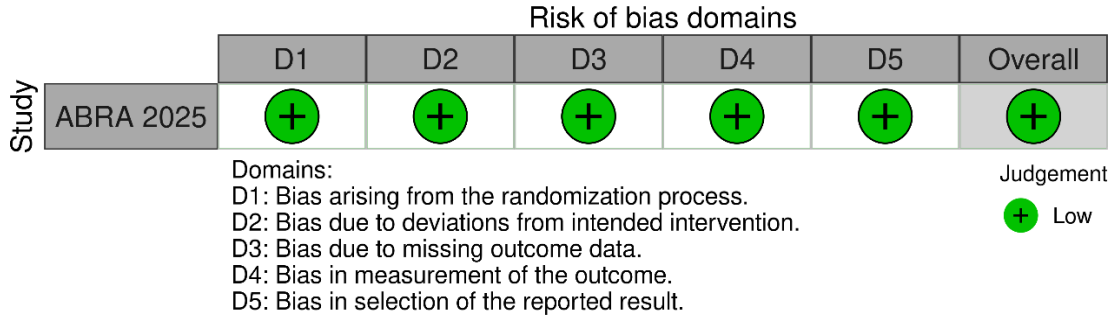
- bias arising from the randomisation process
- bias due to deviations from the intended interventions
- bias due to missing outcome data
- bias in measurement of the outcome
- bias in selection of the reported result.

The included study addressed none of our pre-identified "critical" outcomes. It did address three of our pre-identified "important" outcomes, namely: subsequent exacerbations of any severity; asthma control (using both ACT and ACQ); and quality of life (using AQLQ). As two

different outcome measures were used for asthma control, a total of four outcomes were assessed for risk of bias. Risk of bias was deemed to be low across all five domains for each of the four outcomes (Figure 3.2).

Figure 3.2 ROB 2 assessment for the ABRA study

Assessment for four outcomes in the ABRA study, namely subsequent exacerbations of any severity, asthma control (using ACT and ACQ), and quality of life (using AQLQ)



3.4 Clinical effectiveness

3.4.1 "Critical" outcomes

Death during current visit

Death was part of the primary composite outcome; however, no deaths were reported in any treatment arm.

Intensive care admission during current visit

Not reported.

Ventilation during current visit

Not reported.

Subsequent severe asthma exacerbations requiring emergency department visit/inpatient admission

Subsequent hospitalisations were part of the primary outcome, "treatment failure", which was defined as a composite of death, admission to hospital, and any need for re-treatment requiring systemic glucocorticoids or antibiotics. As admission to hospital was not reported separately, it was not possible to assess the results for that outcome.

3.4.2 "Important" outcomes

Subsequent asthma exacerbation (any severity)

The primary outcome of the study was treatment failure, which was defined as a composite of death, admission to hospital, and any need for re-treatment requiring systemic glucocorticoids or antibiotics, at 90 days. Treatment failures occurred in 74% of the prednisolone only group, compared to 45% in the pooled (benralizumab only and benralizumab and prednisolone) group, which yielded an odds ratio of 0.26 (95% confidence interval (CI) 0.13–0.56). As this composite outcome was not reported separately for asthma and COPD, it did not meet the inclusion criteria for this review.

A secondary outcome in the study was time to treatment failure, expressed as a hazard ratio adjusted for treatment and stratification factors (details of these factors are not reported in the study). This hazard ratio was reported separately for patients diagnosed with asthma, patients diagnosed with COPD, and patients diagnosed with both asthma and COPD. For patients diagnosed with asthma only, the hazard ratio for time to treatment failure within 90 days was 0.44 (95% CI 0.25-0.78) for the pooled intervention groups (benralizumab only and benralizumab plus prednisolone) versus prednisolone only. For patients diagnosed with both asthma and COPD, the hazard ratio for time to treatment failure within 90 days was 0.69 (95% CI 0.16-2.91) for the pooled intervention groups versus prednisolone only.

Length of current stay in hospital, if admitted

Not reported.

Adverse events

Adverse events were reported on an ad-hoc basis during the 90-day follow-up period but not measured as an outcome at a given time-point for all study participants. Results were reported jointly for all patients, with asthma and or COPD. The proportion of patients with at least one adverse event was 91% in the group receiving prednisolone only, 77% in the group receiving benralizumab only, and 75% in the group receiving benralizumab plus prednisolone. Although results were reported jointly for all patients, with asthma and or COPD, further asthma exacerbation was the most commonly reported adverse event, accounting for 43% of reported events. Other adverse events included COPD exacerbation (13%), COVID-19 infection (6%), cough (6%), and sinusitis or sinus infection (6%).

Serious adverse events requiring hospitalisation

As for adverse events, serious adverse events were reported on an ad-hoc basis during the 90-day follow-up period but not measured as an outcome at a given time-point for all study participants. Results were reported jointly for all patients, with asthma and or COPD. Serious adverse events were reported in 6% of patients in the group receiving prednisolone one, 6% in the group receiving benralizumab only, and 2% in the group receiving benralizumab plus prednisolone. It was not clear from the text what constituted a serious adverse event, or if they always required the patient to be hospitalised.

Asthma control

Asthma control was assessed in all patients with an asthma diagnosis, including the small number of patients with a co-existing COPD diagnosis, using ACQ7 (score range 0-7, with a higher score indicating worse disease control) and ACT (score range 5-25, with a higher score indicating better disease control) at 28 and 90 days. The minimally clinical important mean difference for ACT and ACQ7 was 0.5 points. For ACQ7, the mean difference was 0.5 points (95% CI 0.1 to 0.9; p=0.029) for the pooled intervention groups versus prednisolone only at day 28. Statistically significant improvements were not seen for ACT at day 28 (mean difference 1.6 points (95% CI –0.4 to 3.6), p=0.12). No difference between groups was seen at 90 days for either ACQ7 or ACT.

Asthma-related quality of life

Asthma-related quality of life was assessed in all patients with an asthma diagnosis, including the small number of patients with a co-existing COPD diagnosis, using the AQLQ (score range 1-7, with a higher score indicating better disease control). The minimally clinical important difference for AQLQ was 0.5. The mean difference was 0.53 (95% CI 0.04 to 1.02; p=0.035) for the pooled intervention groups versus prednisolone only at day 28. No difference between groups was seen at 90 days. EuroQoL was administered to all patients, regardless of diagnosis, and not reported separately for patients diagnosed with asthma.

3.5 Cost effectiveness

Cost-effectiveness was not addressed in the included study and no other relevant cost-effectiveness study was found during the search.

4 Discussion

The aim of this systematic review was to summarise and evaluate the evidence for clinical and cost-effectiveness of anti-IL-5 therapy when used for the treatment of acute exacerbations of asthma. Anti-IL-5 therapy has been shown in multiple systematic reviews and meta-analyses to be effective in managing severe eosinophilic asthma,[29, 45, 46] and it is currently licensed as an add-on treatment for prevention of asthma exacerbations in this patient group. Further, case reports have begun to appear in the literature advocating for its evaluation in the treatment of acute asthma exacerbation. In this context, it is timely to evaluate the evidence for the use of anti-IL-5s for the treatment of acute asthma exacerbation. An evidence synthesis for a Dutch guideline from 2022 did not locate any trials assessing the clinical effectiveness of anti-IL-5 therapy for acute asthma. Our review identified one recent RCT addressing this question.[44]

It is noteworthy that the patient population studied in the included study was limited to those experiencing an eosinophilic exacerbation, a narrower group than that specified in our review question. Although the intervention of the included study related to treatment delivered at the time of an acute exacerbation, the study outcomes evaluated all concerned the impact of the intervention on the risk of future exacerbations and the impact on patient-reported outcomes (asthma control, quality of life, asthma symptoms) at later follow-up. None of the outcomes reported related to the index acute exacerbation the patient was being treated for. Therefore, no data was available for the two “critical” outcomes for the review: intensive care admissions and ventilation treatment during the index visit. Death was identified as an outcome of the study, however no deaths were recorded in any treatment arm. Finally, although further hospitalisations for asthma exacerbations were part of the primary outcome of the ABRA study, they were part of a composite outcome for treatment failure (also including death and any exacerbations requiring re-treatment with systemic glucocorticoids or antibiotics), which was analysed for asthma and COPD patients combined. The overall risk of treatment failure was 76% lower in the pooled intervention groups compared to control group; however, as subgroup and outcome-specific results could not be extracted, these results could not be used to assess any of the outcomes identified as “critical” for the purpose of this review.

In relation to the "important" outcomes identified for the purpose of this review, the included study reported that the use of anti-IL-5 therapy (administered on its own or with oral prednisolone) reduced the risk of further exacerbations (of any severity but requiring treatment with oral corticosteroids or antibiotics) at 90 days and improved asthma control and asthma-related quality of life at 28 days, compared to oral prednisolone only.

During the course of the systematic review, we located several studies that did not meet our inclusion criteria but which may be of interest. A 2015 study investigated the impact of one dose of benralizumab administered in an outpatient setting after completing initial treatment for an acute asthma exacerbation (eosinophilic or otherwise) and did not find a difference in the proportion of subjects with one or more asthma exacerbation (overall or hospitalised) at 12 weeks when compared to placebo.[47] However, it did find that the intervention group had a reduction in the rate (number per person-years of follow-up) of both asthma exacerbations and exacerbations resulting in hospitalisation when compared to the control group. As the intervention was administered after discharge for an exacerbation, rather than at the time of the acute exacerbation, it did not meet the inclusion criteria for this review. Another RCT registered in 2020 with estimated completion date in 2023 aimed to investigate the initiation of benralizumab at the time of an acute exacerbation with raised blood eosinophil count and for a further 48 weeks.[48] However, we have not been able to locate any publicly available results for this study and the last update to the record was in July 2021.

Although the findings of this systematic review may be encouraging, suggesting a potential use for anti-IL-5 therapy in acute exacerbations in certain populations, these findings must be interpreted with caution and in the context of the limited available research. As only one study met the inclusion criteria, consisting of a sample of 107 individuals with asthma and or COPD exacerbation and high blood eosinophil counts, limited conclusions may be drawn regarding the clinical effectiveness of anti-IL-5 therapy in the context of acute asthma exacerbations. Currently, anti-IL-5s are not licensed for use in acute asthma in any jurisdiction, including Ireland. Additionally, there is no evidence to date evaluating the cost-effectiveness of anti-IL-5 therapy used in this context. The RCT included in the review administered a once-off 100mg dose of benralizumab to the patients in the intervention

arms of the trial. In Ireland, as of August 2025, a 30mg dose of benralizumab is priced at €1,999 and a 100mg dose of mepolizumab at €1,037,[49] making cost an important consideration in the use of these medications. Further additional large RCTs are required to evaluate the potential value of using anti-IL-5 therapy as a component of acute asthma care; however, as of August 2025 there does not appear to be any further clinical trials in progress registered on ClinicalTrials.org.[50]

To our knowledge, this is the most comprehensive and rigorous review to systematically identify and appraise this topic, since the Dutch 2022 search.[35] The review was carried out in accordance with the PRISMA reporting guidance,[36] with a comprehensive search conducted in multiple databases, as well as a backwards-citation and forwards-citation search of all included studies. The outcomes identified as "critical" and "important" for the purpose of the review were chosen in collaboration with the GDG, considering the input of both clinical experts and patient representatives. The absence of a grey literature search may have excluded very recent evidence, however we searched ClinicalTrials.org and did not identify any ongoing trials, thus we consider it unlikely that key evidence has been omitted.

5 Conclusion

This systematic review identified one small study investigating the use of anti-IL-5 therapy in acute exacerbations of asthma with high blood eosinophil counts, which found that patients in the combined intervention groups had a lower risk of subsequent exacerbations at 90 days post-exacerbation, and experienced improved asthma control and quality of life at 28 days. No studies investigating cost-effectiveness were identified. Due to the lack of evidence identified in this review, limited conclusions regarding the potential value of anti-IL-therapy in this context may be made, with further primary research required to inform clinical guidelines.

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Appendices

Appendix 1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1.3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1.4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.3 and appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.4

Section and Topic	Item #	Checklist item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 2.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 2.1
	10b	List and define all other variables for which data were sought (for example, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.6
Effect measures	12	Specify for each outcome the effect measure(s) (for example, risk ratio, mean difference) used in the synthesis or presentation of results.	Section 2.5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (for example, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesise results and provide a rationale for the	NA

Section and Topic	Item #	Checklist item	Location where item is reported
		choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (for example, subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (for example, confidence/credible interval), ideally using structured tables or plots.	Section 3.4

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (for example, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4
	23b	Discuss any limitations of the evidence included in the review.	Section 4
	23c	Discuss any limitations of the review processes used.	Section 4
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4, section 5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Section 2.3 2.5

Appendix 2: Search Strategy

SOURCES SEARCHED

Databases	Number of results	Date searched
Medline Complete via Ovid	120	18/06/2025
Embase via Elsevier	367	18/06/2025
The Cochrane Library	38	18/06/2025
Clinical Trials.gov	11	18/06/2025
Total	536	
Total after duplicates removed	**436**	

Database Name	Medline via Ovid
Date search was run	18 June 2025

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 17, 2025

Search Strategy:

#	Searches	Results
1	Status Asthmaticus/ or acute severe asthma.ti,ab,kf. or severe acute asthma.ti,ab,kf. or status asthmaticus.ti,ab,kf. or (asthma* adj3 (cris?s or shock or state or attack* or exacerbat*)).ti,ab,kf. or ((exp Asthma/ or asthma.ti,ab,kf.) and (Airway Obstruction/ or fatal attack*.ti,ab,kf. or near fatal.ti,ab,kf. or respiratory failure.ti,ab,kf.)) or acute asthma.ti,ab,kf.	22888
2	exp Leukotriene Antagonists/ or Magnesium Sulfate/ or exp Albuterol/ or exp Interleukin-5/ or (leu?otriene adj3 (antagonist* or block* or inhibitor*)).ti,ab,kf. or epsom salt.ti,ab,kf. or magnesium sulfate.ti,ab,kf. or mg longoral.ti,ab,kf. or sulfamag.ti,ab,kf. or sulmetin.ti,ab,kf. or magnesium sulphate.ti,ab,kf. or aero clenil.ti,ab,kf. or aeroclenil.ti,ab,kf. or ah 3365.ti,ab,kf. or ah3365.ti,ab,kf. or albuterol.ti,ab,kf. or almotex.ti,ab,kf. or asmacaire.ti,ab,kf. or asmadil.ti,ab,kf. or asmalin.ti,ab,kf. or asmasal.ti,ab,kf. or asmatol.ti,ab,kf. or asmaven.ti,ab,kf. or asmavent.ti,ab,kf. or asmidon.ti,ab,kf. or asmol.ti,ab,kf. or broncho spray.ti,ab,kf. or broncho-spray.ti,ab,kf. or bronter.ti,ab,kf. or brytolin.ti,ab,kf. or butahale.ti,ab,kf. or buto-asma.ti,ab,kf. or butomix.ti,ab,kf. or butotal.ti,ab,kf. or butovent.ti,ab,kf. or buventol.ti,ab,kf. or cibutamol.ti,ab,kf. or cletal.ti,ab,kf. or cybutol.ti,ab,kf. or dilatamol.ti,ab,kf. or ecovent.ti,ab,kf. or emplusal.ti,ab,kf. or exafil.ti,ab,kf. or farcolin.ti,ab,kf. or frespire.ti,ab,kf. or glisend.ti,ab,kf. or grafalin.ti,ab,kf. or krosalburol.ti,ab,kf. or libretin.ti,ab,kf. or loftan.ti,ab,kf. or mozal.ti,ab,kf. or novosalmol.ti,ab,kf. or parasma.ti,ab,kf. or proventil.ti,ab,kf. or prox-s.ti,ab,kf. or pulmol s.ti,ab,kf. or repetabs.ti,ab,kf. or respolin.ti,ab,kf. or salamol.ti,ab,kf. or salbuair.ti,ab,kf. or salbulin.ti,ab,kf. or salbumol	40613

	fort.ti,ab,kf. or salbupart.ti,ab,kf. or salbutamol.ti,ab,kf. or salbuvent.ti,ab,kf. or salden.ti,ab,kf. or salgem.ti,ab,kf. or salmol.ti,ab,kf. or saltos.ti,ab,kf. or solbutamol.ti,ab,kf. or spacehaler.ti,ab,kf. or sultanol.ti,ab,kf. or venetlin.ti,ab,kf. or ventilan.ti,ab,kf. or ventodisk.ti,ab,kf. or ventodisks.ti,ab,kf. or ventol.ti,ab,kf. or volmac.ti,ab,kf. or benralizumab.ti,ab,kf. or fasenra.ti,ab,kf. or medi 563.ti,ab,kf. or medi563.ti,ab,kf. or bosatria.ti,ab,kf. or mepolizumab.ti,ab,kf. or nucala.ti,ab,kf. or sb 240563.ti,ab,kf. or sb-240563.ti,ab,kf. or sb240563.ti,ab,kf. or cinqaero.ti,ab,kf. or cinqair.ti,ab,kf. or reslizumab.ti,ab,kf. or sch 55700.ti,ab,kf. or sch55700.ti,ab,kf. or actamone.ti,ab,kf. or airathon.ti,ab,kf. or airing.ti,ab,kf. or alvokast.ti,ab,kf. or apilone.ti,ab,kf. or ascafi.ti,ab,kf. or ascolin.ti,ab,kf. or asmenol.ti,ab,kf. or asprevent.ti,ab,kf. or astecon.ti,ab,kf. or asthator.ti,ab,kf. or asthmasan.ti,ab,kf. or asthmont.ti,ab,kf. or astmirex.ti,ab,kf. or astmodil.ti,ab,kf. or atentus.ti,ab,kf. or atlabiclo.ti,ab,kf. or belokast.ti,ab,kf. or brolyt.ti,ab,kf. or castispir.ti,ab,kf. or chesmon.ti,ab,kf. or deprive.ti,ab,kf. or elukan.ti,ab,kf. or elunkast.ti,ab,kf. or eonic.ti,ab,kf. or filkast.ti,ab,kf. or fulmont.ti,ab,kf. or imvlo.ti,ab,kf. or ispyrra.ti,ab,kf. or jepafex.ti,ab,kf. or kipres.ti,ab,kf. or l 706631.ti,ab,kf. or l706631.ti,ab,kf. or lanair.ti,ab,kf. or leukast.ti,ab,kf. or lukair.ti,ab,kf. or lukanof.ti,ab,kf. or lukas aiwa.ti,ab,kf. or lukasm.ti,ab,kf. or lukastang.ti,ab,kf. or lukavent.ti,ab,kf. or melarth.ti,ab,kf. or metigrenul.ti,ab,kf. or milukante.ti,ab,kf. or mintalos.ti,ab,kf. or miralust.ti,ab,kf. or "mk 0476".ti,ab,kf. or mk 476.ti,ab,kf. or mk0476.ti,ab,kf. or mk476.ti,ab,kf. or modrian.ti,ab,kf. or modulair.ti,ab,kf. or mofenstra.ti,ab,kf. or mokast.ti,ab,kf. or molucar.ti,ab,kf. or monalux.ti,ab,kf. or monart.ti,ab,kf. or monast.ti,ab,kf. or moncas.ti,ab,kf. or mondeo.ti,ab,kf. or monkasta.ti,ab,kf. or monlast.ti,ab,kf. or monlucare.ti,ab,kf. or monspes.ti,ab,kf. or monstonol.ti,ab,kf. or montair.ti,ab,kf. or montast.ti,ab,kf. or montecell.ti,ab,kf. or montecon.ti,ab,kf. or montefar.ti,ab,kf. or montegen.ti,ab,kf. or montelair.ti,ab,kf. or montelak.ti,ab,kf. or montelar.ti,ab,kf. or montelex.ti,ab,kf. or montelubronch.ti,ab,kf. or montelucaste.ti,ab,kf. or montelukast*.ti,ab,kf. or montelux.ti,ab,kf. or montemyl.ti,ab,kf. or montep.ti,ab,kf. or monterast.ti,ab,kf. or	

	monteresp.ti,ab,kf. or montespir.ti,ab,kf. or montewin.ti,ab,kf. or montexal.ti,ab,kf. or monthan.ti,ab,kf. or montol.ti,ab,kf. or montus.ti,ab,kf. or moolpas.ti,ab,kf. or nal 6336.ti,ab,kf. or nal6336.ti,ab,kf. or orilukast.ti,ab,kf. or otelus.ti,ab,kf. or pentafeno.ti,ab,kf. or perasm.ti,ab,kf. or pluralais.ti,ab,kf. or pneumo-kast.ti,ab,kf. or promonta.ti,ab,kf. or rasec.ti,ab,kf. or relukas.ti,ab,kf. or respilukas.ti,ab,kf. or romilast.ti,ab,kf. or saslong.ti,ab,kf. or singodem.ti,ab,kf. or singulair.ti,ab,kf. or singulair allergy.ti,ab,kf. or singulair ar.ti,ab,kf. or singulair chew.ti,ab,kf. or singulair mini.ti,ab,kf. or singulergy.ti,ab,kf. or solok.ti,ab,kf. or spirokast.ti,ab,kf. or spiromon.ti,ab,kf. or surfair.ti,ab,kf. or symlukast.ti,ab,kf. or telelux.ti,ab,kf. or telukast.ti,ab,kf. or teluki.ti,ab,kf. or tevalukast.ti,ab,kf. or thordel.ti,ab,kf. or valnuen.ti,ab,kf. or velukast.ti,ab,kf. or xaira.ti,ab,kf. or yekast.ti,ab,kf. or zakomoxit.ti,ab,kf. or interleukin 5 antibody.ti,ab,kf.	
3	1 and 2	2784
4	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	841992

5	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1843443
6	Economics/	27548
7	Cost benefit analysis/	98103
8	"costs and cost analysis"/	52293
9	Cost allocation/	2019
10	Cost control/	21717
11	Cost savings/	13044
12	Cost of illness/	34675
13	Cost sharing/	2827
14	"deductibles and coinsurance"/	1902
15	Medical savings accounts/	552
16	Health care costs/	46450
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18	Drug costs/	18067
19	Employer health costs/	1098
20	Hospital costs/	12374
21	Health expenditures/	25682

22	Capital expenditures/	2005
23	Value of life/	5836
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25	exp economics, medical/	14463
26	Economics, nursing/	4013
27	Economics, pharmaceutical/	3166
28	exp "fees and charges"/	31696
29	exp budgets/	14364
30	(low adj cost).mp.	104245
31	(high adj cost).mp.	23478
32	(health?care adj cost$).mp.	21328
33	(fiscal or funding or financial or finance).tw.	237370
34	(cost adj estimate$).mp.	3042
35	(cost adj variable).mp.	55
36	(unit adj cost$).mp.	3423
37	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	479121
38	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	1063361

39	4 or 5 or 38	3381098
40	3 and 39	1098
41	limit 40 to dt=20220109-20250618	120

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