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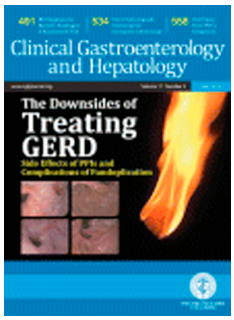

Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review

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Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review

Short Title: Outcomes in EoE RCTs

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Abbreviations: COS (core outcome set), COMET (Core Outcome Measures in Effectiveness Trials), DP (distensibility plateau), EEsAI (Eosinophilic Esophagitis Activity Index), EMA (European Medicines Agency), EoE (eosinophilic esophagitis), eos (eosinophils), EoE-HSS (EoE Histology Scoring System), EREFS (EoE Endoscopic Reference Score), FDA (Food and Drug Administration), FLIP (functional lumen imaging probe), HPF (high power field), IBD (inflammatory bowel disease), IL (interleukin), PPI (proton pump inhibitor), PRO (patient-reported outcome), RCT (randomised controlled trial), TGF (transforming growth factor)

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Abstract

Background & Aims: Agents are being developed for treatment of eosinophilic esophagitis (EoE). However, it is not clear what outcome measures would best determine the efficacy and safety of these agents in clinical trials. We performed a systematic review of outcomes used in randomized placebo-controlled trials of EoE and we estimate the placebo response and rates of remission.

Methods: We searched MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and the EU Clinical Trials Register from inception through February 20, 2018 for randomized controlled trials of pharmacologic therapies for EoE. Efficacy outcome definitions, measurement tools, and the proportion of patients responding to placebo were collected and stratified by based on histologic, endoscopic, and patient-reported outcomes.

Results: We analyzed data from 22 placebo-controlled trials, comprising 1112 patients with EoE. Ten additional active registered trials were identified. Most published trials evaluated topical corticosteroid therapy (13/22, 59.1%). Histologic outcomes measuring eosinophil density and patient-reported outcomes were reported in 21/22 published trials (95.5%). No consistently applied definitions of histologic or patient-reported response or remission were identified. Endoscopic outcomes were described in 60% (12/20) of published trials. The EoE Endoscopic Reference Score is the most commonly applied tool for describing changes in endoscopic appearance. The median histologic response to placebo was 3.7% (range 0%-31.6%) and the median rate of remission in patients given placebo was 0.0% (range 0%-11.0%). The median patient-reported response to placebo was 14.4% (range 8.6%-77.8%) and rate of remission in patients given placebo was 26.2% (range 13.2%-35.7%).

Conclusions: In a systematic review of the literature, we found that no standardized definitions of histologic, endoscopic, or patient-reported outcomes are used to determine whether pharmacologic agents produce a response or remission in patients with EoE. A core outcome set is needed to reduce heterogeneity in outcome reporting and facilitate trial interpretation and comparison of results from trials.

Keywords:

esophagus, inflammation, drug, endoscopy, histology

Background & Aims

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized histologically by eosinophilic infiltration and clinically by symptoms of esophageal dysfunction in the context of an antigen-mediated immune response.[1] Consensus guidelines have established first-line pharmacologic, dietary, and endoscopic treatment for EoE, emphasizing the role of topical corticosteroids, dietary restriction, and endoscopic dilation targeted at improving patient symptoms and reducing histologic eosinophil burden.[2, 3] Topical corticosteroids are the mainstay of drug-based therapy, but there are no US Food and Drug Administration (FDA)-approved treatments and only one orodispersible budesonide formulation has been approved by the European Medicines Agency (EMA) for treatment of EoE.[4, 5] Accordingly, there is great interest in therapeutic development in this field with multiple classes of agents under evaluation.

Several barriers to efficient drug development in EoE exist.[6] Importantly, there is a lack of standardized outcome measures for use in registration trials that can support labelling claims. The FDA mandates that "clinically meaningful" endpoints that measure the way patients feel, function, and survive be used.[7] Therefore, analogous to randomised controlled trials (RCTs) in inflammatory bowel disease (IBD), future EoE clinical trials are likely to incorporate coprimary endpoints featuring both patient-reported outcomes (PROs) and objective inflammatory measures. Nevertheless, there is uncertainty regarding the appropriateness of endpoint definitions and the responsiveness of current disease activity indices in EoE[8] and unsurprisingly, there is lack of consensus on the type of outcomes to measure, the way these outcomes should be defined, and the circumstances in which these outcomes should be assessed.[9]

Developing a core outcome set (COS) is thus a priority in EoE research. A COS is a consensus-derived minimum set of outcomes that should be measured and reported in all clinical trials in a given field.[10] Adoption of a COS minimizes heterogeneity in reporting and potential publication

bias, improves the quality of evidence synthesis, and facilitates comparisons of interventions in meta-analyses. COS development is a multi-step process that involves systematically reviewing the literature to identify current trial endpoints, surveying affected stakeholders, and achieving consensus.[10] A similar COS development initiative is underway in IBD.[11, 12] In addition to selecting appropriate endpoints, understanding the placebo response in clinical trials is critical for efficient drug development. Furthermore, this process facilitates accurate sample size calculations and maximizes assay sensitivity for detecting true differences between active comparator and placebo. Whilst placebo rates in other gastrointestinal disorders have been well characterized,[13-15] placebo rates and the determinants of the placebo response in EoE RCTs require further evaluation. Hirano *et al.* have previously demonstrated in a phase 2 trial of budesonide oral suspension that despite a placebo run-in period, symptom improvement occurred in approximately one quarter of patients randomised to placebo with no baseline demographic features predictive of this response.[16]

To address these limitations, we systematically reviewed all randomised, placebo-controlled RCTs of pharmacologic interventions in EoE. We aim to describe placebo rates in EoE trials, identify relevant endpoints and outcome definitions used in current EoE trials, and establish a conceptual framework by which a COS for future EoE trials can be developed.

Methods

Search Strategy

MEDLINE (Ovid, 1948-2017), Embase (Ovid, 1947-2017), and CENTRAL (1994-2017) were searched without language restriction from inception to February 20, 2018 for RCTs of pharmacologic interventions in EoE. Using the PICO framework, we aimed to capture all studies enrolling patients with EoE regardless of age (patient population), undergoing pharmacologic therapy (intervention), compared against placebo (comparator), and describing any symptom-based, endoscopic, histologic, or exploratory outcomes (outcome). The search strategy is outlined in **Supplemental File 1**. Conference proceedings from Digestive Disease Week and United European Gastroenterology Week (2012-2017) and references of relevant studies and review articles were hand-searched to identify additional studies. Finally, ClinicalTrials.gov and the European Union (EU) Clinical Trials Register were searched for registered, actively recruiting RCTs. Citations and abstracts were screened and complete manuscripts were retrieved for potentially eligible studies. Articles were independently assessed by two investigators (TMN, BvR) and disagreement was resolved by consensus and discussion with a third reviewer (CM). All data were extracted independently and accuracy was verified in a quality control process by a third investigator (CEP).

Study Eligibility Criteria

Studies were eligible for inclusion if they reported a randomised, placebo-controlled trial in patients with EoE that evaluated a pharmacologic intervention. Similar criteria were applied to registered trials on ClinicalTrials.gov and the EU Clinical Trials Register. Studies of children, adolescents, or adults were eligible. However, trials of endoscopic dilation or dietary exclusion therapies, and trials without a placebo comparator arm were excluded. These restrictions were applied to focus this review on pharmacologic interventions, although we recognize that similar challenges with respect to minimizing placebo response and outcome heterogeneity apply to

trials of dietary or endoscopic therapy and non-placebo controlled studies. Separately published *post-hoc* or retrospective analyses of RCTs were not included to avoid duplicate inclusion.

Data Extraction

The primary data extraction included: (1) descriptions of primary and secondary efficacy outcomes, definitions, and measurement tools; (2) descriptions of exploratory outcomes; and (3) the proportion of patients randomised to placebo achieving patient-reported, endoscopic, or histologic response and remission (as defined by the original study authors). Additionally, information regarding trial design (publication year, trial phase, number of treatment arms, trial location and number of trial centres, total participants and participants randomised to placebo, follow-up duration), trial-level patient data (age and gender distribution, proportion on proton pump inhibitor (PPI) therapy at baseline, disease duration), and the active comparator (drug class and route of administration) were collected.

The risk of bias in the published studies was assessed using the Cochrane risk of bias tool, which assesses the following domains: 1) selection bias (random sequence generation, allocation concealment); 2) performance bias (blinding of participants and personnel); 3) detection bias (blinding of outcome assessment); 4) attrition bias (incomplete outcome data); 5) reporting bias (selective reporting); and 6) other sources of bias.[17]

Data Synthesis and Analysis

Standard descriptive statistics were used to describe trial characteristics. A comprehensive inventory of outcomes and definitions was generated through qualitative review and subsequently organized into subdomains (histology, endoscopy, patient-reported outcomes). The proportion of studies reporting each outcome was calculated and stratified by year of publication.

In the initial study protocol, we planned to pool histologic, endoscopic, and patient-reported placebo response and remission rates in meta-analysis using a random-effects model; however, due to the small number of trials and significant heterogeneity in outcome definitions, it was methodologically inappropriate to formally pool reported placebo rates. Additionally, a substantial proportion of trials reported placebo rates of 0% (see **Results**); pooling these studies in meta-analysis, even with a continuity factor, would likely result in biased estimates. Therefore, we generated a descriptive summary of the proportion of placebo responders or remitters where available but without pooled point estimates. For studies reporting quantitative before and after treatment changes in the mean or median scoring index, the percentage change in the placebo group was calculated by dividing the difference in quantitative score after treatment by the scale of the scoring instrument. The median and interquartile range of placebo response and remission rates was calculated and then graphically depicted in box-and-whisker, stratified by outcome domain. All statistical analyses were conducted using STATA 14.2 (StataCorp, College Station, TX: StataCorp LP).

This meta-analysis conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[18]

Results

Search Results and Study Characteristics

The flow diagram for inclusion of trials identified by the literature search is illustrated in **Supplemental Figure 1**. Twenty-two placebo-controlled RCTs[19-40] were identified; another ten registered and enrolling trials were identified through ClinicalTrials.gov and the EU Clinical Trials Register. Baseline study characteristics are summarized in **Table 1**. Most of the published trials were phase II studies (81.8%, 18/22), enrolling adult patients (54.5%, 12/22). Thirteen studies (59.1%, 13/22) compared a corticosteroid preparation against placebo. Ten trials reported concomitant PPI use; the mean proportion of EoE patients receiving concomitant PPI therapy was 57.0% (standard deviation ±26.5%, range 13.2%-100%). The mean follow-up duration was 12.1 weeks (SD ±10.7 weeks, range 2-50 weeks). Risk of bias assessment is summarized in **Supplemental Table 1**; most studies were judged to be at low risk of bias for most domains.

Outcome Reporting

The proportion of trials reporting histologic, endoscopic, and patient-reported outcomes is summarized in **Figure 1**, stratified by year of publication. Both histologic and patient-reported outcomes were described in nearly all reported trials (95.5%, 21/22) and registered studies (90%, 9/10). In contrast, only 13 reported RCTs (59.1%) and four (40%) registered trials defined *a priori* endoscopic endpoints. Exploratory outcomes were evaluated in 68.2% (15/22) of reported RCTs and included: (1) serum or tissue biomarkers (including MIB-1/Ki-67[19], interleukin (IL)-5[22, 25], IL13[25, 27, 35], eotaxin[22, 30], tryptase for mast cells[19, 21, 23, 25, 27, 29], tumor necrosis factor[21, 22], tenascin C[21, 27], cytokeratin[21, 23], terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling positive inflammatory and epithelial cells[21, 23], transforming growth factor beta (TGF-β)[20-23, 25, 27], CD3/8[19, 21-23], eosinophil cationic protein[21-23], eosinophil derived neurotoxin[22, 24], eosinophil peroxidase[27], serum

immunoglobulins[29], and thymic stromal lymphopoietin[35]); (2) esophageal thickness[23] (as measured on endoscopic ultrasound); (3) genetic factors associated with EoE (including single nucleotide polymorphisms of TGF-β[20] and measures of the EoE transcriptome[28, 30]), and (4) esophageal distensibility measures as assessed by functional lumen imaging probe (FLIP).[38]

Histology Outcome Definitions

Definitions of histology outcomes for reported RCTs are summarized in **Table 2** and for registered RCTs in **Table 3**. Most trials defined histology outcomes using eosinophil density as defined most commonly by peak eosinophil counts although no consistent thresholds for defining histologic response or remission were used. Furthermore, the definition of peak eosinophil count varied depending on field size, number of HPFs evaluated, and from which level of the esophagus samples were obtained. For histologic remission, peak eosinophil thresholds ranged from 0 to 6 eosinophils/high power field (HPF); for histologic response, peak eosinophil count thresholds ranged from 5 to 24 eosinophils/HPF. Fourteen studies reported change in absolute eosinophil counts before and after therapy or by percentage changes from baseline in eosinophil density.[23, 24, 26-30, 32, 33, 35, 37-40] One study used the EoE Histology Scoring System (EoE-HSS) to evaluate both severity and extent of eight features (eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis).[38] Four studies specified that histologic outcomes required changes at multiple esophageal levels (e.g. proximal and distal esophagus).[19, 28, 30, 31]

Endoscopy Outcome Definitions

Definitions of endoscopy outcomes for reported RCTs are summarized in **Table 2** and for registered RCTs in **Table 3**. Several authors used non-validated changes in overall or global

endoscopic appearance with descriptions of classic EoE endoscopy findings (such as linear furrows, white exudates, and esophageal rings). Two studies used a visual analogue scale[27, 33] and four studies used the EoE Endoscopic Reference Score (EREFS).[32, 36-38] The EREFS is the only endoscopic outcome instrument that has undergone inter- and intra-observer validation in both North American and European studies. The EREFS is also the most commonly used measurement tool for endoscopy outcomes in registered trials (4 studies, 40%). No consistently used thresholds for endoscopy scores were identified to determine endoscopic response/remission; rather, changes compared to baseline were commonly reported.

Patient-Reported Outcome Definitions

Definitions of patient-reported outcomes for reported RCTs are summarized in **Table 2** and for registered RCTs in **Table 3**. Multiple different scoring systems, mostly non- or only partially validated, have been used to assess patient-reported response or remission. These include the Mayo Dysphagia Questionnaire[24, 30, 34], the Dysphagia Symptom Questionnaire[36], the EoE Activity Index (EEsAI)[40], patient or physician global assessments of disease severity[26, 32, 37, 40], the Dysphagia Score (also termed the Straumann Dysphagia Index)[21-23], the EoE Clinical Symptom Score[28, 31], the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)[20], and the Visual Dysphagia Questionnaire.[27] As with endoscopy and histology endpoints, no uniformly applied thresholds for patient-reported remission or response have been identified although the complete absence of symptoms has been used by some authors to define remission. Health-related quality of life was not specifically defined as a treatment endpoint in any of the currently published RCTs.

Histology, Endoscopy, and Patient-Reported Placebo Rates

Placebo rates in EoE RCTs are summarized in **Figure 2** and **Table 4**, presented as either: (1) proportion of patients achieving response/remission defined by the original study authors; or (2)

396 percentage change in before and after treatment disease activity scores relative to the scale of
397 scoring index when placebo response was reported as a continuous variable. The median
398 histologic placebo response rate was 3.7% (range 0% to 31.6%). Two studies reported
399 histologic placebo response or partial remission rates of >20%. Both studies used an eosinophil
400 density cutoff of <20 eos/HPF (<65 eos/mm^2 HPF).[23, 33] The median histologic placebo
401 remission rate was 0.0% (range 0% to 11.0%). Eight studies reported histologic placebo
402 remission rates of 0%.[20, 21, 23, 24, 28, 33, 39, 40] When assessed as a continuous measure relative to
403 the scale of the measurement tool, endoscopy scores before and after placebo administration
404 changed between -0.6% to -16%. Larger variances were evident when assessing patient-
405 reported placebo response (**Figure 2**): patient-reported scores before and after placebo
406 administration varied between -28.6% to +36.6. The median symptomatic response rate was
407 14.4% (range 8.6% to 77.8%); the median symptomatic remission rate was 26.2% (range 13.2%
408 to 35.7%).

409

Discussion

Over the past two decades, clinical trials of therapeutic agents in EoE have evolved from retrospective case series with symptom-based outcomes to prospective, randomised, placebo-controlled trials that include both valid patient-reported outcomes and objective measures such as histopathology and endoscopy. In this systematic review of all reported and registered placebo-controlled trials of pharmacologic therapies for EoE, we describe the placebo response and summarise the outcome measures used in existing and planned RCTs. We found that histologic placebo response and remission rates in EoE trials are relatively low compared to RCTs in other gastrointestinal disorders, although there is greater variance in patient-reported placebo responses. We also highlight the significant heterogeneity in outcome measurement and outcome definitions used in current studies for histology, endoscopy, and patient-reported endpoints and there is no consensus on thresholds for defining response or remission.[9] Development of a COS that standardises outcome measurement and reporting in EoE RCTs is thus a priority.

Potential determinants of the histologic placebo response in EoE RCTs include: 1) inclusion of patients with PPI-responsive EoE who derive both clinical and histologic benefits from concomitant PPI therapy[41]; 2) sampling of histologically normal mucosa in the context of patchy eosinophilic infiltration in EoE; 3) regression to the mean; and 4) spontaneous changes in disease activity in the natural history of EoE, possibly as a response to fluctuations in allergen or dietary exposures. Although symptomatic placebo rates in EoE tend to be lower than in other allergic and gastrointestinal disorders,[42, 43] they still remain higher and more variable compared to histologic placebo response. Some EoE studies report greater than one third to one half of placebo patients achieving response or remission using patient-reported endpoints.[23, 31, 36] Symptomatic placebo rates may be influenced by dietary avoidance or modifications that reduce dysphagia or by endoscopic dilation at baseline if not precluded by the study entry criteria. However, this discrepancy between histologic and symptomatic placebo response also

436 underscores the discordance between patient-reported symptoms and objective measures of
437 disease activity: in an international cohort study of 269 EoE patients, an Eosinophilic
438 Esophagitis Activity Index (EEsAI) patient-reported outcome score of ≤15 points identified only
439 67.2% of patients with endoscopic and histologic remission.[44]
440
441 Additionally, histologic endpoints defined by eosinophil density may not closely correlate with
442 patient-reported outcomes because dysphagia symptoms and risk of food impaction in EoE are
443 driven primarily by complications of esophageal remodeling, rather than mucosal
444 inflammation.[45, 46] Histologic outcomes are assessed in nearly all EoE RCTs defined by either
445 peak or mean eosinophil count per HPF. Although this paradigm is attractive because it
446 provides a quantitative measure of inflammatory burden, several potential pitfalls exist. First,
447 variability in results may be influenced by technical factors such as the cross-sectional area of
448 the microscope manufacturer (correctable by using normalised density to eosinophils per mm^2)
449 and by sampling differences in the number and location of acquired biopsies.[47-49] Second,
450 mucosal biopsies may underestimate the full extent of histologic involvement in EoE given that
451 eosinophilic infiltration is not confined to the superficial mucosa, eosinophil density does not
452 necessarily correlate with eosinophil degranulation or function, and other histologic features
453 such as basal cell hyperplasia, mast cell infiltration, and subepithelial fibrosis are not
454 captured.[50, 51]
455
456 To address some of these potential limitations of peak eosinophil density as a measure of
457 disease activity in EoE, Collins *et al.* have developed and validated an EoE Histology Scoring
458 System (EoE-HSS), based on eight features (eosinophil density, basal zone hyperplasia,
459 eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial
460 alteration, dyskeratotic epithelial cells, and lamina propria fibrosis), graded and staged using a
461 four point scale.[52] Future studies should assess the responsiveness to change of this instrument

after a therapeutic intervention. Furthermore, adoption of blinded central reading to minimize observation bias at both enrolment and outcome ascertainment has gained traction in IBD. Although a single pathologist frequently evaluates histologic endpoints in current EoE RCTs, proper assessment inter- and intra-rater reliability using multiple blinded central readers for EoE histopathology endpoints is needed before this is routinely incorporated in clinical trials.

Patient-reported outcomes will likely be an essential component of future registration trials in EoE based upon existing precedents in both ulcerative colitis and Crohn's disease, whereby co-primary endpoints of PROs and objective assessment of inflammation (endoscopy) have been mandated. Although multiple scoring systems have been used to assess dysphagia symptoms in EoE RCTs most have not been validated in this disease. Two disease-specific, validated symptom scoring systems have recently been developed. The Dysphagia Symptom Questionnaire was developed from patient focus groups and primarily assesses frequency and intensity of dysphagia symptoms, with demonstrated responsiveness in an RCT of budesonide oral suspension.[36] The EEsAI was prospectively developed and validated for use in adults with EoE and additionally captures food avoidance and behavioral modifications,[53] a common source of reduced quality of life in EoE patients, particularly among those with previous food bolus impactions. Notwithstanding that eating behaviors such as careful mastication, prolonged meal times, and dietary restriction may not be adequately captured by assessment of dysphagia symptoms alone, both indices are candidate measurement tools for evaluating patient-reported outcomes in future RCTs.

Endoscopic outcomes offer another potential objective treatment target in EoE RCTs. Earlier studies used non-validated global assessments of endoscopic appearance based on common EoE features. Development of the EoE Endoscopic Reference Score (EREFS), which incorporates both major (fixed rings, exudates, furrows, edema, stricture) and minor features

(crepe paper esophagus) has been an important advance.[54] The items for the EREFS were identified through a literature review and a grading scheme was developed through consensus expert opinion. Internal validation, based on evaluation of a sampling of videos by 21 endoscopists with diverse experience and practice patterns, demonstrated moderate to good interobserver reliability. The EREFS is the proposed endoscopic endpoint in four registered RCTs, but it still requires further external validation, particularly evaluating the role of central blinded endoscopy reading and comparison of video versus still-image endoscopic assessment on reliability performance characteristics.[55]

Although histologic, endoscopic, and symptom-based outcomes have traditionally been used to assess EoE activity, there has been growing interest in quantifying and targeting esophageal distensibility as a measure of end organ remodeling. Functional lumen imaging probe (FLIP) uses impedance planimetry to quantify esophageal distention.[6] Lower distensibility plateaus (DP) are associated with food bolus impaction and the need for esophageal dilation.[45] In contrast, dietary and medical therapies have been demonstrated to improve DPs and this reduction correlates with better symptomatic outcomes.[56] In a recent phase 2 placebo-controlled RCT, treatment with dupilumab, a humanised anti-IL-4Rα monoclonal antibody, improved esophageal distensibility and highlighted the potential of FLIP as a responsive biomarker to medical therapy.[38]

Understanding outcome definitions in clinical trials is crucial for translating evidence-based research to clinical practice. Indeed, many of the newer EoE disease activity indices such as the EoEHSS, EEsAI, and EREFS have not yet been routinely incorporated in daily care. It is important for physicians to recognize that heterogeneity in outcome definitions used in clinical trials may influence interpretations of response to therapy. As the patient's treatment goals are typically resolution of dysphagia symptoms, avoidance of food bolus impactions, prevention of

long-term disease complications, and ultimately, optimization of quality of life, these are parameters should be captured in outcome definitions for use in RCTs. Additionally, choosing appropriate histologic and endoscopic targets will help dictate therapeutic decisions in clinical practice: for example, targeting more stringent histologic endpoints (<5 eos/hpf vs. <15 eos/hpf)[57] or endoscopic resolution[58] is associated with improved treatment response and symptom alleviation.

Our study has some limitations. First, we included only placebo-controlled RCTs and a substantial proportion of the EoE literature is rooted in observational studies and non-controlled trials. Thus, there may be outcomes of interest that are not captured in this review. Second, we excluded trials of endoscopic therapies or dietary interventions. We restricted the inclusion specifically to RCTs investigating pharmacologic therapies because the focus of COS development will be primarily applicable to RCTs of novel therapeutic compounds. However, similar symptom-based and histologic outcomes are measured in both prospective and retrospective observational studies of dietary interventions in EoE, with heterogeneity in the defined thresholds for response and remission remaining an important challenge.[59-63] A previous systematic review has also evaluated outcomes after endoscopic dilation for EoE[64]: efficacy was typically assessed using dysphagia scoring systems although there is an increased focus on safety outcomes, particularly with respect to esophageal perforation. Finally, we could not pool placebo rates to generate single point estimates. However, it is considered methodologically inappropriate to pool studies with such heterogeneity in outcome definitions, leading to a potentially biased point estimate that is not representative of the literature. Thus, we have presented the median as a measure of central tendency with ranges rather than a pooled point estimate.

The next steps in COS development have been outlined in the Core Outcome Measures in Effectiveness Trials (COMET) handbook.[65] First, input from relevant stakeholders, including patients, health care providers, trialists, regulators, industry representatives, health policy-makers, and researchers, will be sought. Next, relevant outcome domains will be defined. We propose that a similar framework to that presented in this review be considered, wherein a coprimary endpoint incorporating a patient-reported outcome measure and an objective histologic or endoscopic outcome in accordance with regulatory requirements be adopted. A consensus on specific outcome definitions and thresholds will be achieved through a multi-round Delphi process that permits anonymized feedback to participants. Finally, the COS will be ratified and disseminated for implementation in future RCTs.

CONCLUSION

In conclusion, choosing appropriate treatment endpoints is crucial for clinical trial design. Outcomes should be relevant, valid, support regulatory and labelling claims, and correlate with meaningful changes in quality of life and disease course. In EoE, this translates to improvements in patient-reported symptoms, histologic burden of inflammation, and possibly reversal or prevention of fibrostenotic EoE complications. Although there has been significant progress in clinical trial research in EoE over the past two decades, we identify the substantial heterogeneity in outcome definitions in this field. Many instruments for EoE outcome assessment have only recently been developed and additional RCT data applying these instruments is required to adequately define response and remission cutoffs using anchor-based methods. This systematic review serves as a conceptual framework for COS development in EoE.

563 **Tables and Figures Legend**

564 **Table 1.** Baseline study characteristics

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570 esophagitis placebo-controlled clinical trials

571

572 **Figure 1.** Endpoint reporting in eosinophilic esophagitis placebo-controlled clinical trials,
573 stratified by year of publication

574 **Figure 2.** Box-and-whisker plots for histologic, endoscopic, and symptom-based placebo
575 response and remission in eosinophilic esophagitis clinical trials.

576

577 **Supplemental File 1.** Search strategy

578 **Supplemental Figure 1.** PRISMA diagram

579 **Supplemental Table 1.** Risk of bias assessment

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764

765 **Table 1.** Baseline study characteristics

766

	n = 22
Trial Participants (n)	
Total randomised participants	1112
Participants randomised to placebo	410
Trial Phase (n, %)	
Phase I	2 (9.1)
Phase II	18 (81.8)
Phase III	2 (9.1)
Trial Publication Year (n, %)	
2006-2010	4 (18.2)
2011-2015	9 (40.9)
2016-2017	9 (40.9)
Active Comparator (n, %)	
Corticosteroid	13 (59.1)
Biologic Agent	6 (27.3)
Other	3 (13.6) †
Trial Population (n, %)	
Pediatric/adolescent	5 (22.7)
Adult	12 (54.5)
Mixed	5 (22.7)
Patient Characteristics	
Mean participant age (years, SD)	25.8 (13.6)
Mean disease duration (years, SD)	4.1 (1.9)
Mean percentage of enrolled males (%, SD)	69.0 (14.1)
Mean percentage of concurrent PPI (% SD)	57.0 (26.5)
Follow-up (weeks, SD)	
Mean follow-up duration	12.1 (10.7)

767

768 † One trial of montelukast, one trial of prostaglandin D2 receptor CRTH2 antagonist, one trial of
769 cromolyn sodium

770 **Table 2.** Histology, endoscopy, and symptom-based endpoints in published eosinophilic esophagitis placebo-controlled clinical trials

771

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Konikoff 2006[19]	Fluticasone 12 weeks	Response: peak eosinophil count >1 and <24 eos per 400x HPF, in both proximal and distal esophagus Remission: peak eosinophil count <1 eosinophil in all 400x HPFs in both proximal and distal esophagus	Presence of endoscopic furrowing, epithelial hyperplasia	Presence of clinical symptoms (abdominal pain, vomiting, dysphagia)
Dohil 2010[20]	Budesonide 12 weeks	Response: peak eosinophil count 7-9 eos/HPF Remission: peak eosinophil count 0-6 eos/HPF Change in epithelial histology, lamina propria histology, and lamina propria fibrosis	Change in endoscopy scoring tool (mucosal pallor/reduced vasculature, linear furrows/mucosal thickening, white plaques, concentric rings/stricture, friability/"tissue-paper" mucosa	Change in symptom scoring tool (heartburn/regurgitation, abdominal pain, nausea/vomiting, anorexia/early satiety, dysphagia, symptom-induced nocturnal wakening, gastro-intestinal bleeding)
Straumann 2010a[21]	Budesonide 2 weeks	Response: 5-20 eos/HPF Remission: <5 eos/HPF	Change in endoscopic appearance (white exudates, red furrows, corrugated rings, solitary ring, crepe-paper sign, severe stenosis)	Response: reduction in clinical symptom score ≥3 points compared to baseline using patient-reported outcome (frequency of dysphagia, intensity of dysphagia)
Straumann 2010b[22]	Mepolizumab 34 weeks	Response: peak eosinophil count <5 eos/HPF	Change in endoscopic appearance (minor: fine nodules, fine whitish reticular structures, furrows; moderate: bright white scale- or plaque-like structures, corrugated rings; or severe: mucosal lesions, fixed stenosis)	Patient-reported Dysphagia Score (frequency of dysphagia, intensity of dysphagia, score 0-9)

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Straumann 2011[23]	Budesonide 50 weeks	Remission: mean eosinophil count <5 eos/HPF (measured in 40 HPF) Partial remission: mean eosinophil count 5-20 eos/HPF	Endoscopic ultrasound (thickness of mucosa, submucosa, muscularis propria)	Patient-reported Dysphagia Score (frequency of dysphagia, intensity of dysphagia, score 0-9)
Alexander 2012[24]	Fluticasone 6 weeks	Complete response: >90% reduction in mean eosinophil count (from 5 HPF) Partial response: >50% reduction in mean eosinophil count	Resolution of all endoscopic findings	Complete response: answer of "no" to all questions by Mayo Dysphagia Questionnaire (MDQ-30) Partial response: decrease in severity of at least 2 levels
Ghaffari 2012[†25]	Beclomethasone 8 weeks	Tissue cytokine staining	Not reported	Not reported
Spergel 2012[26]	Reslizumab 15 weeks	Percentage change in peak eosinophil count	Not reported	Change in Physician's Eosinophilic Esophagitis Global Assessment (physical findings, vital signs, predominant eosinophilic esophagitis symptom assessment, patient's symptom diary, dietary questions)
Straumann 2013[27]	Prostaglandin D2 receptor CRTH2 antagonist 8 weeks	Reduction in esophageal eosinophil load (mean eosinophil count in 40 HPF)	Global appearance of endoscopic appearance using 10cm visual analogue scale	Combination visual dysphagia questionnaire (VDQ 0-36), chest pain questionnaire (0-9) PRO
Butz 2014[28]	Fluticasone 6 months	Complete remission: ≤1 eos/HPF in proximal and distal esophagus Response: peak eosinophil count ≤6 eos/HPF, peak ≤14 eos/HPF, mean eosinophil count ≤1 eos/HPF, mean eosinophil count ≤2 eos/HPF, decrease in eosinophil count ≥90-95%	Not reported	EoE Symptom Score (vomiting, nausea, abdominal pain, dysphagia, heartburn, chest pain, regurgitation, food impactions, early satiety, poor appetite)

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Clayton 2014[29]	Omalizumab 16 weeks	Reduction in esophageal eosinophil content (maximum eos/HPF)	Not reported	Change in dysphagia score (0-6 Likert scale)
Rothenberg 2014[30]	Anti-IL13 (QAX576) 6 months	75% reduction in peak eosinophil count in proximal and distal esophagus	Not reported	Change in Mayo Dysphagia Questionnaire (eosinophilic esophagitis relevant questions, MDQ-30)
Gupta 2015[31]	Budesonide 12 weeks	Response: peak eosinophil count ≤6 eos/HPF in all esophageal levels (composite outcome with clinical outcomes) Remission: peak eosinophil count ≤1 eos/HPF in all esophageal levels	Not reported	Symptom response: >50% reduction in Eosinophilic Esophagitis Clinical Symptom Score (EoE CSS) Symptom resolution: EoE CSS of 0
Hirano 2016[†32]	Anti-IL13 (RPC4046) 16 weeks	Response: change in mean eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Daily Symptom Diary (DSD), EEsAI PRO, and Subject's Global Assessment of Disease Severity
Miehlke 2016[33]	Budesonide 2 weeks	Response: mean eosinophil count <65 eos/mm^2 HPF Remission: mean eosinophil count <16 eos/mm^2 HPF	Change in endoscopic intensity score (white exudates, furrows, oedema, fixed rings, crepe paper sign, short segment stenosis, long-distance stenosis, 0-21) Global assessment of endoscopy appearance using 100mm visual analogue scale	Response: decrease in Dysphagia Score ≥3 (frequency of dysphagia, intensity of dysphagia, score 0-9)
Alexander 2017[34]	Montelukast 26 weeks	Not reported	Not reported	Symptom remission: absence of dysphagia as measured by dysphagia frequency, severity, and food impaction questions from the Mayo Dysphagia Questionnaire, 2-week version

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Bhardwaj 2017[35]	Beclomethasone 8 weeks	Response: change in peak eosinophil count	Not reported	Symptom response: reduction in dysphagia, heartburn, abdominal pain, and other symptoms
Dellon 2017[36]	Budesonide 12 weeks	Response: ≤6 eos/HPF	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire (DSQ, 0-84), ≥30% reduction in DSQ, ≥50% reduction in DSQ
Hirano 2017a[†37]	Fluticasone (oral disintegrating tablet) 8 weeks	Change in median eosinophil count	Improvement in endoscopic features as measured by the EoE Endoscopic Reference Score (EREFS)	Improvement in Patient Global Assessment of Disease Severity (PatGA), EEsAI PRO
Hirano 2017b[†38]	Dupilumab 12 weeks	Change in overall peak eosinophil count, response (peak eosinophil <6 eos/hpf, <15 eos/hpf) Change in EoE Histological Scoring System	Change in EoE Endoscopic Reference Score (EREFS)	Response: reduction in Straumann Dysphagia Index ≥3 points Response: reduction in EEsAI PRO by ≥40%
Liebermann 2017[†39]	Cromolyn sodium Follow-up not reported	Change in peak eosinophil count Remission: complete resolution of eosinophilia	Not reported	Symptom reduction by symptom score (not further specified)
Lucendo 2017[†40]	Budesonide 6 weeks	Remission: clinicopathological remission (not further specified) Change in peak eosinophil count	Rate of endoscopic normalization Change in total modified EEsAI endoscopic instrument score	Remission: EEsAI-PRO ≤20 Remission: resolution of dysphagia and pain during swallowing Time to first symptom resolution, change in Patient's and Physician's Global Assessment of EoE Activity Score

[†]Results reported in abstract form

EEsAI (Eosinophilic Esophagitis Activity Index), Eos (eosinophils), HPF (high power field), PRO (patient-reported outcome)

775 **Table 3.** Histology, endoscopy, and symptom-based endpoints in registered eosinophilic esophagitis placebo-controlled clinical trials

776

Study (Clinicaltrials.gov	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
NCT02113267 EudraCT 2012-005842-39	Mometasone 8 weeks	Not reported	Not reported	Change in Watson Dysphagia Scale Score (WDS) Change in EORTC QLQ-OES18 Dysphagia Scale (eating scale and choking item) Global health/social functioning dimensions of SF-36
NCT02605837	Oral budesonide suspension 16 weeks	Response: peak eosinophil count ≤6 eos/HPF Change in peak eosinophil count, change in histopathologic epithelial features (by central reviewer)	Change in EoE Endoscopic Reference Score (EREFS)	Symptom response: ≥30% reduction in Dysphagia Symptom Questionnaire combined score Change in pain with swallowing
NCT01702701	Montelukast 12 weeks	Change in esophageal eosinophilia	Not reported	Improvement in Dysphagia Symptom Score
NCT03191864 EudraCT 2016-004749-10	APT-1011 12 weeks	Response: peak eosinophil count ≤6 eos/HPF (from 5-6 biopsies from proximal and distal esophagus) Response: percentage of patients with peak eosinophil count <1 eos/HPF, <15 eos/HPF Sustained response (histology response maintained at week 12, 26, and 52)	Change in EoE Endoscopic Reference Score (EREFS)	Change in baseline Global EoE Symptom Score Change in number of dysphagia episodes at baseline
NCT02873468	Fluticasone 8 weeks	Change in eosinophilic infiltration (not further specified)	Not reported	Not reported
NCT02371941	Cromolyn sodium 2 months	Change in peak esophageal eosinophil count	Not reported	Change in symptom score by Pediatric Esophagitis Symptom

Study (Clinicaltrials.gov	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
				Score
NCT02019758	Budesonide Fluticasone 8 weeks	Change in maximum eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire
NCT02493335	Budesonide orodispersible tablet 48 weeks	Rate of patients with histological relapse	Not reported	Rate of patients free of treatment failure Rate of patients with clinical relapse
NCT02736409	Oral budesonide suspension 36 weeks	Change in peak eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire
EudraCT 2005-006074-10	Mepolizumab 12 weeks	Reduction in peak eosinophil count to <5 eos/HPF	Not reported	Frequency and severity of eosinophilic esophagitis-related pain, regurgitation, vomiting, swallowing disorders, feeding difficulties

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779 **Table 4.** Histology, endoscopy, and symptom-based placebo and active comparator rates in published eosinophilic esophagitis

780 placebo-controlled clinical trials

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Konikoff 2006[19]	Response: 20.0% (3/15) Remission: 6.7% (1/15)	Response: 55.0% (11/20) Remission: 50.0% (10/20)	NR	NR	NR	NR
Dohil 2010[20]	Response: 0.0% (0/9) Remission: 0.0% (0/9) Δ mean peak eosinophil count: -18.3 eos/HPF	Response: 6.7% (1/15) Remission: 86.7% (13/15) Δ mean peak eosinophil count: -61.9 eos/HPF	Δ mean endoscopy score: -16.0% (-2.4/15)	Δ mean endoscopy score: -20.7% (-3.1/15)	Δ mean symptom scoring tool: -6.4% (-0.9/14)	Δ mean symptom scoring tool: -16.4% (-2.3/14)
Straumann 2010a[21]	Response: 0.0% (0/18) Remission: 11.1% (2/18) Δ mean eosinophil count: -5.8 eos/HPF	Response: 16.7% (3/18) Remission: 72.2% (13/18) Δ mean eosinophil count: -62.7 eos/HPF	NR	NR	Δ mean symptom score: -6.8% (-0.61/9)	Δ mean symptom score: -37.7% (-3.39/9)
Straumann 2010b[22]	Δ mean peak eosinophil count: -2.7 eos/HPF	Δ mean peak eosinophil count: -39.4 eos/HPF	NR	NR	NR	NR
Straumann 2011[23]	Partial remission: 28.6% (4/14) Remission: 0.0% (0/14) Δ mean eosinophil count: +64.3 eos/HPF	Partial remission: 14.3% (2/14) Remission: 35.7% (5/14) Δ mean eosinophil count: +31.4 eos/HPF	NR	NR	Remission: 35.7% (5/14) Δ mean symptom score: +36.6% (+3.29/9)	Remission: 64.3% (9/14) Δ mean symptom score: +16.7% (+1.5/9)
Alexander 2012[24]	Response: 0.0% (0/21)	Response: 61.9% (13/21)	Remission: 4.8% (1/21)	Remission: 26.7% (4/15)	Response: 33.3% (7/21)	Response: 57.1% (12/21)

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
					Remission: 28.6% (6/21)	Remission: 42.9% (9/21)
Ghaffari 2012[†25]	NR	NR	NR	NR	NR	NR
Spergel 2012[26]	NR	NR	NR	NR	Δ mean physician's EoE global assessment score: -11.4% (-1.14/10) Δ mean EoE predominant symptom assessment score: -14.4% (-1.44/10)	Δ mean physician's EoE global assessment score: -11.2% (-1.12/10) Δ mean EoE predominant symptom assessment score: -12.8% (-1.28/10)
Straumann 2013[27]	Δ mean eosinophil count: -3.3 eos/HPF	Δ mean eosinophil count: -41.6 eos/HPF	Δ mean global endoscopy assessment score: -0.6% (-0.06/10)	Δ mean global endoscopy assessment score: -3.6% (-0.36/10)	Δ mean Visual Dysphagia Questionnaire: -18.9% (-6.82/36)	Δ mean Visual Dysphagia Questionnaire: -15.8% (-5.71/36)
Butz 2014[28]	Remission: 0.0% (0/13)	Remission: 65.2% (15/23)	NR	NR	NR	NR
Clayton 2014[29]	Δ mean eosinophil count: -4 eos/HPF	Δ mean eosinophil count: -2 eos/HPF	NR	NR	Δ dysphagia score: -25.2% (-1.7/6)	Δ dysphagia score: -20.0% (-1.2/6)
Rothenberg 2014[30]	Response: 12.5% (1/8)	Response: 40.0% (6/15)	NR	NR	NR	Response: 66.7% (10/15)
Gupta 2015[31]	Response: 5.6% (1/18)	Response: 94.1% (16/17)	NR	NR	Response: 77.8% (14/18) Remission: 33.3% (6/18)	Response: 52.9% (9/17) Remission: 17.6% (3/17)
Hirano 2016*[32]	Δ mean eosinophil count: -4.4 eos/HPF	Δ mean eosinophil count: -99.9 eos/HPF	Δ mean EREFS score: -4.5% (-0.9/20)	Δ mean EREFS score: -24.0% (-4.8/20)	Δ Daily Symptom Diary score: -7.6% (-6.4/84)	Δ Daily Symptom Diary score: -15.8% (-13.3/84)
Miehlke 2016[33]	Response: 31.6% (6/19) Remission: 0.0% (0/19) Δ mean eosinophil count: -30 eos/HPF	Response: 94.7% (18/19) Remission: 89.5% (17/19) Δ mean eosinophil count: -287 eos/HPF	Response: 26.3% (5/19) Δ mean total endoscopic abnormality score: -3.3% (-0.7/21)	Response: 57.9% (11/19) Δ mean total endoscopic abnormality score: -16.8% (-3.4/21)	Δ mean dysphagia score: -28.6% (-2.0/9)	Δ mean dysphagia score: -20.0% (-1.8/9)

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Alexander 2017[34]	NR	NR	NR	NR	Remission: 23.8% (5/21)	Remission: 40.0% (8/20)
Bhardwaj 2017[35]	Δ eosinophil count: -25.3 eos/HPF	Δ eosinophil count: -50.7 eos/HPF	NR	NR	NR	NR
Dellon 2017[36]	Response: 2.6% (1/38) Δ peak eosinophil count: -17.3 eos/HPF	Response: 38.8% (19/49) Δ peak eosinophil count: -117.0 eos/HPF	Δ mean EREFS score: 2.0% (0.4/20)	Δ mean EREFS score: -19.0% (-3.8 /20)	Response: 44.7% (17/38) Remission: 13.2% (5/38) Δ mean Dysphagia Symptom Questionnaire: -8.9% (-7.5/84)	Response: 69.4% (34/49) Remission: 20.4% (10/49) Δ mean Dysphagia Symptom Questionnaire: -17.0% (-14.3/84)
Hirano 2017a†[37]	Δ median eosinophil count: -136 cells/mm^2 HPF	Δ median eosinophil count: -355 cells/mm^2 HPF	Δ median EREFS score: -7.5% (-1.5/20)	Δ median EREFS score: -17.5% (-3.5/20)	Δ mean global assessment: -5.0% (-0.5/10)	Δ mean global assessment: -25.0% (-2.5/10)
Hirano 2017b†[38]	Response: 0.0% (0/24) for both <6 and <15 eos/HPF Δ peak eosinophil count: -7.4 eos/HPF Δ Histology Scoring System (HSS) grade: +3.9% Δ Histology Scoring System (HSS) stage: -3.5%	Response: 60.9% (14/23) for <6 eos/HPF and 78.3% (18/23) for <15 eos/HPF Δ peak eosinophil count: -94.1 eos/HPF Δ Histology Scoring System (HSS) grade: -64.2% Δ Histology Scoring System (HSS) stage: -58.1%	Δ median EREFS score: -1.5% (-0.3/20)	Δ median EREFS score: -9.5% (-1.9/20)	Response: 12.5% (3/24) by Straumann Dysphagia Index, 8.3% (2/24) by EEsAI PRO Δ Straumann Dysphagia Index: -14.4% (-1.3/9) Δ EEsAI: -11.3% (-11.3/100)	Response: 39.1% (9/23) by Straumann Dysphagia Index, 26.1% (6/23) by EEsAI PRO Δ Straumann Dysphagia Index: -33.3% (-3.0/9) Δ EEsAI: -34.6% (-34.6/100)
Lieberman 2017†[39]	Remission: 0.0% (0/7)	Remission: 11.1% (1/9) Δ mean peak eosinophil count: -11.6 eos/HPF	NR	NR	Δ Symptom Score: -30.7% (-9.9/32.2)	Δ Symptom Score: -58.8% (-22.3/37.9)

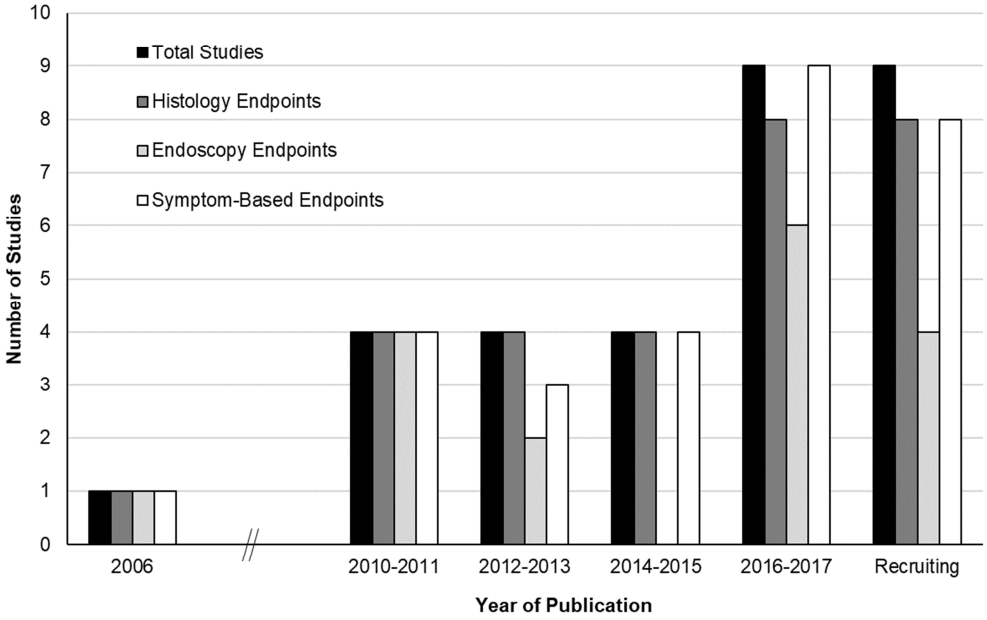
Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Lucendo 2017[†40]	Remission: 0.0% (0/29) Δ mean peak eosinophil count: -4 eos/mm^2 HPF	Remission: 93.2% (55/59) Δ mean peak eosinophil count: -226 eos/mm^2 HPF	Remission: 0.0% (0/29)	Remission: 61.0% (36/59)	Remission: 13.8% (4/29) Δ mean patient global assessment: -19.0% (-1.9/10)	Remission: 59.3% (35/59) Δ mean patient global assessment: -38.0% (-3.8/10)

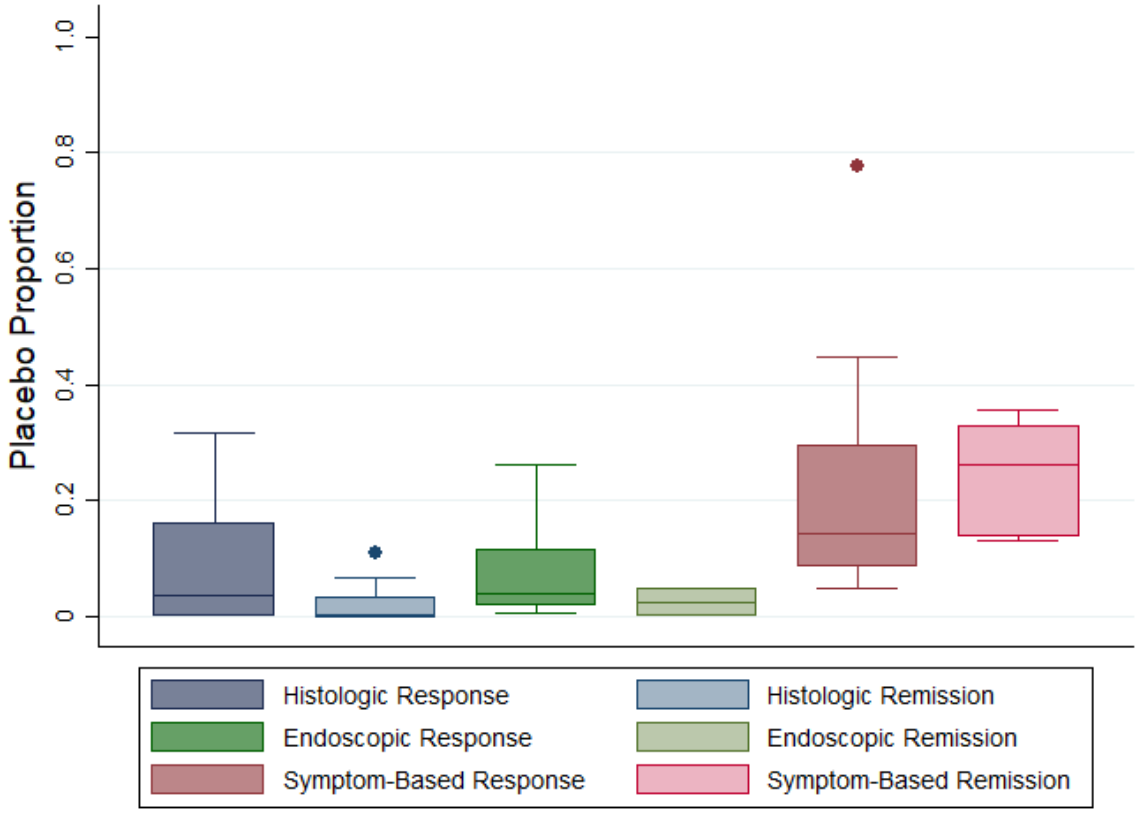
For trials with multiple active comparators, results reported for highest administered dose

[†] Results reported in abstract form

EEsAI EoE Activity Index, HPF high power field, HSS Histology Scoring System, NR not reported, eos eosinophils, EREFS EoE Endoscopic Reference Scoring System

Δ Change in pre- and post-treatment mean score in the placebo group, percentage change calibrated to scale of measurement instrument





Supplemental File 1. Search strategy

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 not 15
17. eosinophilic esophagitis.mp. or exp eosinophilic esophagitis/
18. (eosinophil* and esophag*).mp.
19. (eosinophil* and oesophag*).mp.
20. or/17-19
21. 16 and 20

EMBASE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. eosinophilic esophagitis.mp. or exp eosinophilic esophagitis/
22. (eosinophil* and esophag*).mp.
23. (eosinophil* and oesophag*).mp.

24. or/21-23
25. 20 and 24

Cochrane Central Register of Controlled Trials

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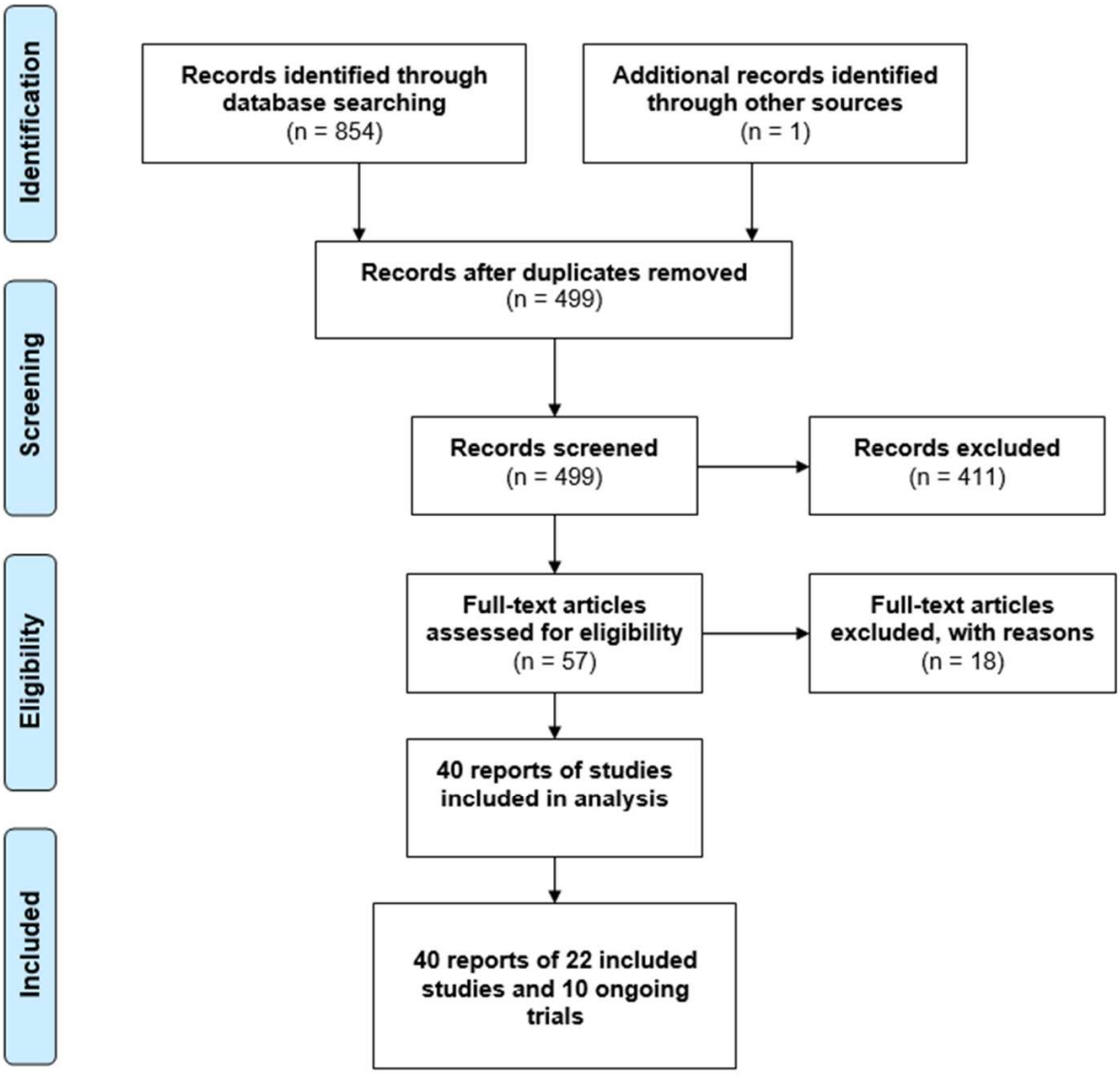
2. eosinophilic oesophagitis
3. or/1-2



Supplemental Figure 1. PRISMA diagram

Supplemental Table 1. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Konikoff 2006	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Dohil 2010	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Straumann 2010a	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Straumann 2010b	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Straumann 2011	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Alexander 2012	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Spergel 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Straumann 2013	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Butz 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Clayton 2014	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Rothenberg 2014	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Gupta 2015	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	High risk	Low risk
Miehlke 2016	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk
Alexander 2017	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Bhardwaj 2017	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Dellon 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk