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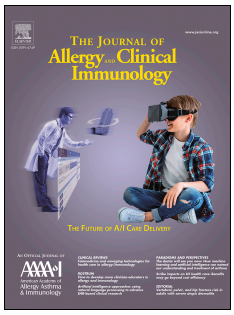

Development of a Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis (COREOS)

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KEY MESSAGES

- Developing a core outcome set (COS), a minimum set of outcomes to be reported in all controlled and observational studies in children and adults with EoE, is important for improving clinical trial design and evidence synthesis;
- This international COS consensus exercise identified tools to be used to standardize disease activity assessment in EoE.

CAPSULE SUMMARY

This COS will be directly applicable to randomized controlled trials and observational studies of novel therapies currently in development for EoE, facilitate evidence synthesis, and allow for comparisons across different therapies.

KEYWORDS

Eosinophilic esophagitis; outcomes; clinical trials; endpoints; histology; histopathology; endoscopy; symptoms; patient reported outcomes; quality of life.

ABBREVIATIONS

COMET, Core Outcome Measures in Effectiveness Trials; COS, core outcome set ; COS-STAD, the Core Outcome Set-STAndards for Development; COS-START, the Core Outcome Set-STAndards for Reporting; EoE, eosinophilic esophagitis; EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoEHSS, EoE Histologic Scoring System; EoE-QoL-A, EoE Quality of Life for adults; EREFS, Endoscopic Reference Score; hpf, high-power field; PedsQL, Pediatric Quality of Life Inventory; PEESS, Pediatric EoE Symptom Score; RCT, randomized controlled trial.

ABSTRACT

Background: Endpoints used to determine treatment efficacy in eosinophilic esophagitis (EoE) have evolved over time. With multiple novel therapies in development for EoE, harmonization of outcomes measures will facilitate evidence synthesis and appraisal when comparing different treatments.

Objective: To develop a core outcome set (COS) for controlled and observational studies of pharmacologic and diet interventions in adult and pediatric patients with EoE.

Methods: Candidate outcomes were generated from systematic literature reviews and patient engagement interviews and surveys. Consensus was established using an iterative Delphi process, with items voted on using a 9-point Likert scale and with feedback from other participants to allow score refinement. Consensus meetings were held to ratify the outcome domains of importance and the core outcome measures. Stakeholders were recruited internationally and included adult and pediatric gastroenterologists, allergists, dieticians, pathologists, psychologists, researchers, and methodologists.

Results: The COS consists of four outcome domains for controlled and observational studies: histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life (QoL). A total of 69 stakeholders (response rate 95.8%) prioritized 42 outcomes in a two-round Delphi process and the final ratification meeting generated consensus on 33 outcome measures. These included measurement of the peak eosinophil count, EoE Histology Scoring System, EoE Endoscopic Reference Score, and patient-reported measures of dysphagia and QoL.

Conclusions: This interdisciplinary collaboration involving global stakeholders has produced a COS that can be applied to adult and pediatric studies of pharmacologic and diet therapies for EoE, which will facilitate meaningful treatment comparisons and improve the quality of data synthesis.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease, characterized histologically by esophageal eosinophil-predominant inflammation and clinically by symptoms of esophageal dysfunction.[1] Since its initial description in the early 1990s, there has been a significant increase in the incidence of EoE, and prevalence rates from population-based studies estimate that approximately 50-100 per 100,000 persons are affected.[2] The diagnosis of EoE is based on both symptoms consistent with esophageal dysfunction, particularly dysphagia in adolescents and adults, as well as the presence of histologic inflammation, defined as a peak eosinophil count (PEC) ≥15 eosinophils per high power field (HPF), with exclusion of other causes of esophageal eosinophilia.[3] Untreated EoE can progress to the development of fibrostenotic complications such as strictures and endoscopically impassable rings, which are associated with progressive symptoms, food impaction, and poor quality of life.[4-6]

Consensus treatment recommendations for EoE have historically included: 1) elimination diets that restrict exposure to potential food allergens; 2) endoscopic dilation for fibrostenotic complications; 3) proton pump inhibitors; and 4) swallowed topical corticosteroids that reduce eosinophilic inflammation.[7, 8] However, these approaches have inherent limitations. Patients must adhere to substantial lifestyle changes for dietary strategies to be effective, dilation carries procedural risks and does not address the underlying inflammatory pathophysiology, and proton pump inhibitors are not effective in all EoE patients. A lack of approved esophageal-specific formulations in many jurisdictions, potential treatment-related side effects, and short duration of efficacy limit the potential of using swallowed topical corticosteroids long-term for managing a chronic disease that almost universally recurs after treatment cessation.[9-11] Accordingly, there has been tremendous interest in developing EoE-specific pharmacotherapies,[12] with over 50 active or enrolling interventional studies for the treatment of EoE registered on Clinicaltrials.gov. Furthermore, recent positive results from phase III trials of dupilumab, a monoclonal antibody

targeting the IL-4 receptor alpha, budesonide orodispersible tablets as both induction and maintenance therapy, and budesonide oral suspension, have inspired even greater enthusiasm for drug development in this field.[13-16]

Despite these breakthroughs, a major limitation to efficient drug development in EoE has been the lack of standardized outcome measures for use in both registrational trials that can support labelling claims and in observational studies that can answer practice-based questions.[17] Although validated, reliable, and responsive instruments of EoE disease activity exist,[18-27] agreement on the most appropriate endpoints for use in clinical studies has not been reached, and significant heterogeneity exists in the outcome measures that are reported.[28] Given the lack of consensus and the increasing scrutiny on outcome measures in clinical trials of EoE, developing a core outcome set (COS) is a research priority. A COS is a consensus-derived minimum set of outcomes that should be measured and reported in all trials in a given therapeutic area.[29] COS development focuses on identifying relevant and appropriate endpoints through an iterative, data-driven process involving all major stakeholders, including researchers, clinicians, and patients. Advantages of adopting a COS include improving the efficiency of clinical studies by ensuring appropriate endpoints are measured, minimizing heterogeneity in outcome reporting, reducing risk of publication bias, improving the quality of evidence synthesis, and facilitating fair comparisons across different therapies.

Therefore, in collaboration with the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), the European Eosinophilic Esophagitis Research Network (EUREOS), and with individuals recruited from the Eosinophil Gastrointestinal Disorders (EGID) Committee of The American Academy of Allergy, Asthma, and Immunology (AAAAI), we aimed to develop an international consensus COS for use in studies of pharmacologic and dietary interventions for adult and pediatric patients with EoE (COREOS).

METHODS

Scope and protocol registration

The COREOS initiative is registered with Core Outcome Measures in Effectiveness Trials (COMET) (www.comet-initiative.org) and was conducted in accordance with the guidelines outlined in the COMET handbook and the standards established by the Core Outcome Set-STAndards for Development (COS-STAD).[29, 30] This manuscript was drafted based on the Core Outcome Set-STAndards for Reporting (COS-STAR) Statement.[31] The patient study was approved by the ethics committee at the University of Lausanne (CER-VD 148/15).

The scope of this COS is to include all pharmacologic and dietary therapies, in both controlled trials and observational studies, for pediatric and adult patients with EoE. Although endoscopic dilation is an important component of management for patients with EoE, the measurement of treatment success post-dilation, including procedural and technical success, is fundamentally different from evaluating therapeutic efficacy of pharmacologic or dietary strategies. We evaluated outcomes for observational studies separately from those in controlled trials, which are typically conducted in different settings, using different methods, and with different levels of study funding and logistical support. These factors are relevant for the feasibility of measuring certain outcomes.

Overview of COS Development

The COS was developed using a multiphase approach summarized in **Figure 1**. First, systematic reviews of the literature and patient engagement surveys were conducted to identify candidate outcomes that have either been previously measured and/or are important to patients with EoE. Next, we used this information to build a framework of different outcome domains. Working groups for each domain were assembled to review the literature for relevant endpoints, and a Delphi survey was conducted to categorize these domains into core, important, and research agenda domains, based on the Outcome Measures in Rheumatology (OMERACT) model.[32] Core

373 outcome domains were carried forward into the next phase. In phase 3, a comprehensive list of
374 outcome measures within each of the core domains was evaluated by a panel of multidisciplinary
375 experts in a two-round Delphi survey to establish consensus. Finally, a virtual ratification meeting
376 was held to vote on the final outcomes included in the COS.
377
378 **Participants**
379 We gathered input from a diverse range of adult and pediatric patients with EoE to determine their
380 values and opinions on the importance of different outcomes.[33] Patients (and caregivers of
381 pediatric patients) were recruited using purposive sampling from multiple clinics to capture a
382 range of disease duration, disease activity (including both symptomatic and asymptomatic
383 patients), disease experiences, and treatment experiences (including patients who had previously
384 been exposed to proton pump inhibitors, swallowed topical corticosteroids, dilation, and dietary
385 exclusion). We focused on engaging patients early in phase 1 of this COS development to
386 determine the appropriate outcome domains for measurement.
387
388 In phase 2 and phase 3, we targeted a minimum sample size of 50 respondents for each Delphi
389 survey. A diverse participant pool was identified and invited by the lead and senior investigator,
390 and included gastroenterologists, pathologists, allergists, researchers, dieticians, psychologists,
391 and methodologists. Selected participants reflected a broad range of clinical knowledge and
392 geographical experience. Panelists were required to have expertise in EoE, demonstrated by
393 peer-reviewed publications or clinical experience in managing adult or pediatric EoE patients.
394
395 **Phase 1: Outcome Identification**
396 Three systematic reviews were conducted to ensure that we comprehensively evaluated the
397 literature with respect to the scope of this COS: 1) a systematic review to assess the operating
398 properties of evaluative indices used in EoE[34]; 2) a systematic review to assess the outcome

399 measures used in RCTs in EoE[28]; and 3) a systematic review to assess the outcome measures
400 used in observational studies in EoE (including studies of topical corticosteroids, dietary
401 measures, and endoscopic dilation). In addition, a systematic review to assess the outcome
402 measures used in pediatric RCTs was previously published by Rubin *et al*.[35] Although dilation
403 was outside the scope of this COS, we specifically searched for outcomes used in studies of
404 endoscopic dilation to ensure that potentially relevant endpoints were not missed. In summary,
405 searches were conducted in MEDLINE, Embase, the CENTRAL Cochrane Library,
406 ClinicalTrials.gov, and/or the EU Clinical Trials Register to identify relevant studies. Evaluative
407 indices and outcomes used to measure treatment efficacy were identified.
408
409 Swiss patients with EoE were engaged to identify their perspective on relevant outcomes for
410 measurement. Patient participation consisted of semi-structured interviews and paper-based
411 surveys, aimed at assessing the relative importance of different treatment goals and outcome
412 measures in EoE. Semi-structured interviews were conducted with EoE patients and used to
413 create a patient survey list of short- and long-term outcomes of importance for therapeutic
414 efficacy. The survey was then distributed to patients with EoE to determine the ranked importance
415 of different outcomes in the following domains: symptoms, quality of life, endoscopy, and
416 histology.
417
418 **Phase 2: Outcome Domains**
419 The information identified from the systematic reviews and patient engagement surveys was used
420 to construct a framework of 11 outcome domains. A Delphi survey was distributed to all experts
421 to identify which domains were of importance to include in the COS. Each domain was ranked on
422 a 9-point Likert scale, based on the Grading of Recommendations Assessment, Development,
423 and Evaluation (GRADE) working group definitions.[36] Scores of 1-3 indicate an outcome domain
424 that was not considered important for inclusion, scores of 4-6 indicate an outcome domain that

was considered important but not critical for inclusion, and scores of 7-9 indicate an outcome domain felt critical for inclusion in the COS. An option to select "unsure of significance or unable to score" was also available. *A priori*, outcome domains scored in the 7-9 range by ≥70% of panelists and in the 1-3 range by <15% of panelists were carried forward to phase 3 as core domains. Working groups consisting of experts in each domain were organized and met by teleconference to review the relevant endpoints. These outcome domains were discussed in a moderated, in-person meeting that occurred at Digestive Disease Week 2019 (San Diego, United States). Outcomes that did not meet the threshold for core domains were reviewed and those with limited available evidence on their use in EoE were assigned as research agenda domains.

Phase 3: Core Outcome Set Voting

A comprehensive list of outcomes identified within each core domain, as well as measurement tools and definitions, were included in an online two-round Delphi survey. Participants were asked to rank each outcome on a 9-point Likert scale as described above, with a specific focus on ranking the most important outcomes for inclusion. Free text entry was available so participants could provide clarification, suggest wording changes, recommend additional endpoints, or provide compelling rationale and arguments for inclusion or exclusion of certain items. Each round was open for 8 weeks to ensure all participants had adequate time to complete the survey.

Responses from the first round were analyzed and collated into a feedback report. Descriptive statistics were used to summarize the number of participants scoring each outcome and the distribution of scores. All open-ended responses were reviewed by the lead and senior investigators to evaluate substantial arguments and additional suggestions. Responses from Round 1 were used to determine the outcomes carried forward to Round 2 based on rules established *a priori*. Outcomes scored in the 7-9 range by ≥50% of the panelists and 1-3 range by <15% of the panelists were carried forward. These definitions have been previously used in

COS exercises and were aimed at mitigating the risk of panelist fatigue.[29] All panelists who completed the Round 1 survey were invited to participate in Round 2 and received an individualized feedback report summarizing both their initial voting results and the results from the group. Panelists were then asked to rescore each outcome on the same 9-point Likert scale, with consideration based on insights from the group. Outcomes scored in the 7-9 range by ≥70% of the panelists and in the 1-3 range by <15% of the panelists were decided to have met consensus for inclusion. Outcomes scored in the 1-3 range by ≥70% of the panelists and in the 7-9 range by <15% of the panelists were defined to have met consensus for exclusion.

We recognize that it is implausible for any single panelist to be completely familiar with every scoring system/grading tool evaluated in this consensus: this was mitigated by: 1) choosing a multidisciplinary panel; 2) panelists were instructed not to answer questions with which they were unfamiliar; and 3) consensus definitions are based on the proportion of respondents. Analysis of missing data suggests that specialists performing endoscopy drove decisions for endoscopic findings, specialists following adult patients drove decisions for symptoms and QoL outcomes in adults, and specialists following pediatric patients drove decisions for symptoms and QoL outcomes in pediatric populations.

Phase 4: Final COS Ratification and Consensus Definitions

A moderated teleconference to ratify the final COS was conducted December 8, 2020. Although this was initially planned as a face-to-face meeting with all stakeholder groups to discuss all items from the Round 2 survey, this was amended to a virtual meeting due to COVID-19 public health restrictions. We elected to discuss only those items that had a reasonable likelihood of being included in the COS: assuming a binomial distribution, outcomes for which the upper 95% confidence interval of the proportion of panelists voting in the 7-9 category exceeded 70% were carried forward to discussion in the ratification meeting. Logistically, it was infeasible for every

panelist voting in the Delphi surveys to participate in the ratification teleconference given the international participation; however, as per the COMET recommendations, representatives from every discipline were present and the ratification panel was similar in composition to the Delphi panelists. Panelists were shown the results from Round 2 voting and the criteria for inclusion were reviewed. All items, including those with consensus, were discussed to ensure that any compelling arguments for or against inclusion were heard and reviewed. After discussion, panelists voted on items anonymously. In this ratification round, voting was simplified to “Include in the COS”, “Do not include in the COS”, or “Unsure”. Items receiving ≥70% of votes in the “Include in the COS” category and <15% of votes in the “Do not include in the COS” category were ratified for final inclusion.

RESULTS

Participants

A total of 36 adult patients with EoE participated in the semi-structured interviews, and paper-based surveys were completed by 109/148 (73.6%) patients.[33] The mean age was 50.2 years (± standard deviation SD 14.5 years) with a mean disease duration of 7.7 years (± SD 4.7 years). Seventy-eight percent of patients (85/109) were male and approximately one third (33.9%, 37/109) had previously experienced a food bolus impaction. A total of 30.3% (33/109) of patients were on proton pump inhibitors, 62.4% (68/109) were on swallowed topical corticosteroids, and 11.0% (12/109) were on elimination diets. Pediatric patients and their caregivers were separately surveyed: 30 patients >11 years and 15 patients <11 years were included. Among pediatric patients, 80.0% (36/45) had associated atopic conditions, 71.4% (25/35) were treated with swallowed topical corticosteroids and 25.7% (9/35) were on an elimination diet.

Demographic characteristics of the expert panelists in each of the Delphi rounds are summarized in **Table 1**. Members of CEGIR, EUREOS, and individuals recruited from the EGID committee of AAAAI were invited to participate in COREOS exercise. A total of 66, 69, and 62 experts participated in the Outcome Domains survey, Round 1 COS survey, and Round 2 COS survey, respectively. The response rates were 95.8% [69/72] and 89.9% [62/69] for Round 1 and 2 surveys, respectively. Twenty-seven participants attended the Phase 4 ratification videoconference. Across all rounds, there were participants from multiple specialties and 16 different countries.

Phase 1: Outcome Identification Systematic Reviews and Patient Engagement

Detailed results from the systematic reviews have been previously published; the major findings are summarized here. In the first review of disease activity indices and their operating properties, 4,373 citations were evaluated to identify 130 eligible studies. The adult EoE Quality of Life (EoE-

QoL-A) questionnaire, EoE Histologic Scoring System (EoEHSS), EoE Endoscopic Reference Score (EREFS), symptom-based Eosinophilic Esophagitis Activity Index (EEsAI) patient-reported outcome (PRO) instrument, Dysphagia Symptoms Questionnaire (DSQ), Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0), and Pediatric Quality of Life Inventory EoE were identified as indices that were either reliable, responsive, or valid measures of disease activity.[34] In a second review of outcome measures used in RCTs, 22 placebo-controlled trials including 1,112 patients with EoE were evaluated, with substantial heterogeneity in the definitions of histologic, endoscopic, and PRO-based response and remission.[28] The use of histologic endpoints was associated with the lowest rate of placebo response.

A third review of outcome measures used in observational studies (including cohort, case series, randomized open-label trials, and case-control studies) was conducted. A total of 59 studies including 3,248 adult EoE patients were included. Histologic, endoscopic, and patient-reported symptom-based endpoints were the most frequently reported, although no consistent definitions of response or remission were identified. Esophageal eosinophil density was the most frequently reported outcome, with varying thresholds for response/remission ranging from 5 to 15 eos/hpf. Endoscopic outcomes were assessed in 43 studies (76.7%) although a formal scoring system such as the EREFS was not routinely used. Similarly, there was substantial heterogeneity in instruments used for measuring symptom-based responses. In addition to the EEsAI and DSQ, other tools that have been used included the Mayo Dysphagia Questionnaire, Dysphagia Frequency Scale, Watson Dysphagia Score, Straumann Dysphagia Index, and multiple, non-validated ad-hoc scores based on different combinations of the frequency, intensity, and/or duration of dysphagia, food bolus impaction, abdominal or chest/retrosternal pain, heartburn, regurgitation, and/or lifestyle modifications.

In the patient engagement surveys, patients considered improvement in EoE-related symptoms and QoL as the most important endpoints: over 90% of patients chose improvement in symptoms and disease-specific QoL as highly important outcomes both in the short- and long-term. Reduction in endoscopic and histologic inflammation were also considered important outcomes, although more so in the long-term rather than the short-term (89.9% vs. 72.9% for endoscopic and 81.3% vs. 61.7% for histologic outcomes, respectively).[33] Among pediatric patients, over 90% of both caregivers and patients ranked symptom and QoL improvement as important short- and long-term therapeutic goals, and over 80% attributed importance to achieving short- and long-term histologic endpoints.

Phase 2: Outcome Domains

Using the information from phase 1, we created a framework of three major categories of outcome domains: 1) clinician-reported domains (including histopathology, endoscopy, esophageal distensibility, immunologic dissection, genetic profiling, and biomarkers); 2) patient-reported domains (including patient-reported symptoms, patient-reported quality of life, and patient perception of health), and 3) other domains (including secondary impact on caregivers and resource utilization). The importance of each domain for inclusion in a COS was reviewed in working groups and then in a face-to-face meeting. A Delphi survey was then distributed to expert panelists and four outcome domains were voted as critical for inclusion (**Table 2** and **Figure 2**): patient-reported symptoms, EoE-specific QoL, histopathology, and endoscopy. The other domains were considered either important but optional at this time, or domains for the research agenda that require additional investigation.

Phase 3: Core Outcome Set Voting

A total of 122 items across the four core outcome domains were included in the Round 1 Delphi survey, which was completed by 69 panelists. Results from Round 1 survey are summarized in **Supplemental Table 1**. These items were organized by outcome domain (58 items for

565 histopathology, 28 items for endoscopy, 24 items for patient-reported symptoms, and 12 items for
566 EoE-specific QoL) and stratified by study type (randomized controlled trials vs. observational
567 studies) and patient population (adult vs. pediatric). All free-text responses were reviewed and
568 incorporated into the second round of voting. A total of 59 outcomes (18 for histology, 12 for
569 endoscopy, 19 for patient-reported symptoms, and 10 for EoE-specific QoL) were included in the
570 Round 2 survey. Results from Round 2 survey are summarized in **Supplemental Table 2.**
571
572 **Phase 4: Ratification Meeting and Core Outcome Set**
573 A total of 42 items from the Round 2 survey were discussed and voted on in the ratification
574 meeting and two additional items were introduced after panel discussion. After voting, 33 items
575 were included in the final COS, summarized in **Table 3**.
576 *COS: Histopathology Outcomes*
577 With respect to histopathology outcomes, there was consensus that the PEC should be reported
578 in all RCTs and observational studies, expressed either as eosinophils (eos)/hpf (including exact
579 area used and the hpf size reported in mm^2) or as eos per mm^2, viewed at 400 × magnification.
580 Several panelists identified that both measures should be reported, as eos/hpf has been
581 historically used in the literature whereas eosinophils per mm^2 adjusts for potential differences in
582 microscope ocular field size. There was consensus that histologic remission should be reported
583 in all studies. However, the precise threshold for histologic remission was debated. There was
584 consensus that the proportion of patients with < 15 eos/hpf in all esophageal locations should be
585 reported in both RCTs and observational studies; there was no consensus on using a more
586 stringent threshold of ≤ 6 eos/hpf, even for RCTs. In RCTs, the EoEHSS should be used, and
587 both the grade and stage of each component item reported.
588
589 *COS: Endoscopy Outcomes*

The panel voted that the EREFS should be used in both RCTs and observational studies to standardize endoscopic assessment of EoE disease activity, scoring the most severe grade of EoE-associated features. Additionally, both inflammatory and fibrotic components of the EREFS should be reported. In the Round 1 survey, different versions of the EREFS were explored: 1) scoring from 0-9 as originally proposed; 2) scoring from 0-8 (with furrows scored as absent/present); 3) vs. scoring from 0-16 (i.e., a 0-8 score summed for two different esophageal locations); and 4) 0-18 using alternative weighting of the different components. Following the *a priori* defined rules for moving items to the next round, only the EREFS scored from 0-8 was carried forwards to Round 2, because of a higher proportion of panelists voting to not include other versions of the EREFS. However, there was extensive discussion that scoring from 0-8 may result in a narrower dynamic range of the EREFS score and decrease responsiveness measured by endoscopy. Additionally, if scoring is performed on a 0-9 scale, *post-hoc* analysis collapsing the categories for moderate-to-severe furrows can generate an EREFS score on a 0-8 scale, but not vice versa. In an *ad hoc* vote, 14/21 (66.7%) panelists favored using the EREFS from 0-9 whereas 7/21 (33.3%) panelists favored using the EREFS from 0-8. Given that this voting was held outside the defined methods of COS development, reporting the original EREFS is optional, if the individual components are provided, so that readers can collapse the furrows grading to generate a comparable score on the 0-8 scale. For both RCTs and observational studies, there was consensus that endoscopic remission should be defined based on the EREFS using a cutoff of ≤ 2. It is worth keeping in mind that whilst the endoscopic EREFS-based remission definition as an EREFS score ≤ 2 was derived based on EREFS scoring from 0 to 8 and from 0 to 9, the endoscopic inflammatory EREFS-based remission defined as the inflammation-associated components (exudate, edema, furrows) score ≤ 2 is based on EREFS scoring from 0 to 8.

COS: Patient-Reported Symptoms

There was consensus that validated instruments for patient-reported symptoms, including the DSQ and the EEsAI, should be assessed in EoE RCTs. However, there was discussion that the initial rounds of the Delphi surveys were completed prior to guidance released from the United States Food and Drug Administration (FDA), which highlight the use of clinical outcome assessment instruments that use daily assessments. The EEsAI was developed and has previously been used in RCTs with a 7-day recall period as secondary endpoint, and this outcome was voted to be included in the COS, recognizing that there was preference from the US FDA for use of an instrument with a 24-hour recall period. The 24-hour EEsAI was added as an item for voting due to the discussion but did not meet the criteria for consensus (**Supplemental Table 3**). There was also consensus that the language used to query dysphagia in adults with EoE include trouble swallowing and delayed/slow passage of food. While "food being stuck" did meet the consensus thresholds in Round 2 of the Delphi voting, it did not reach consensus thresholds in the ratification round as experts identified that this should be more appropriately used for defining food bolus obstruction. No instruments for measuring symptom severity reached consensus for use in observational studies.

Separate instruments were considered for pediatric patients. In pediatric trials, there was consensus that symptoms should be measured using the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0) for RCTs, but not for observational studies.

COS: Quality of Life

There was consensus that QoL should be measured in EoE RCTs using the EoE-specific QoL questionnaire (EoE-QOL-A) for adults and the Pediatric Quality of Life Inventory (PedsQL) EoE Module for pediatrics. When using the PedsQL EoE Module, it was considered appropriate for both parent-proxy report and child self-report to be reported in RCTs. The panel discussed that it was ideal to use disease-specific QoL measures rather than generic QoL measures for this

641 domain. No instruments for use in all observational studies met the consensus threshold for
642 inclusion in the COS.
643

DISCUSSION

In this multidisciplinary, international collaboration between multiple stakeholder groups, we developed a COS to standardize outcome reporting in therapeutic studies of pharmacologic and diet interventions in EoE. We identified four critical outcome domains (histopathology, endoscopy, patient-reported symptoms, and EoE-specific QoL) that are important to patients, clinicians, and researchers, and which reflect the clinicopathologic hallmarks of the disease. Through multiple group discussions and several rounds of voting, we identified measurement tools that should be used to standardize disease activity assessment, both in controlled and observational studies. We took into consideration the appropriateness and validity of different endpoints, feasibility of measurement, and relative importance of different outcomes to each stakeholder. The application of this COS should improve the quality of research in EoE and serve as an impetus for improving clinical care by encouraging clinicians to assess core outcomes of treatment success.

This COS will be directly applicable to randomized controlled trials of novel therapies currently in development for EoE. However, the panel recognized that important elements of trial design, including outcome selection, will depend on who is conducting the trial (investigator- vs industry-initiated) and the subsequent regulatory requirements for labeling claims. During the development of this COS, the US FDA released guidance for EoE clinical trials.[37] Key takeaways included the selection of EoE-related symptoms and histology as co-primary endpoints, use of a clinical outcome assessment instrument based on daily recall, and defining histologic remission based on having ≤ 6 eos/hpf in all biopsies. The similarities but also differences between the FDA guidance with these independent recommendations reported herein are notable. Although the COS does not precisely map onto this regulatory guidance, our framework of measuring patient-reported symptoms and histopathology as core domains is complementary, and also extends to observational studies. Moreover, we included EoE-specific QoL as an important domain of measurement, particularly for patients, and endoscopic assessment as not only an important tool

for clinicians to directly visualize the esophageal mucosa, but also a prerequisite to obtaining biopsy samples.

Given the importance of eosinophilic inflammation in defining EoE, it was not surprising that histopathology was almost universally agreed upon as a core domain. However, three areas of controversy garnered more discussion. First, the panel reviewed the reporting of peak eosinophil density based on eos/hpf vs. eos/mm^2. Although using eos/mm^2 was felt to be advantageous for standardizing density measurements across different microscopes and field sizes,[38] most of the literature to date has expressed the PEC per hpf, and there was consensus that this should continue to be measured and reported to facilitate historical treatment comparisons and ensure interpretability. However, the panel felt it was feasible to report both measures and recognized that particularly for RCTs, standardization of field size analysis was crucial to achieve. Therefore, we advocate for a greater emphasis on reporting eos/mm^2 (using remission definitions of PEC ≤25 eos/mm^2 and <60 eos/mm^2, corresponding to PEC of ≤6 eos/hpf and <15 eos/hpf, respectively).

Second, there was consensus that a PEC of <15 eos/hpf should be used as the threshold to define histologic remission, although this is discordant from the FDA recommendations. Historically, multiple cut-off points have been used to define EoE, ranging from 5-30 eos/hpf.[39] However, the data to support the use of these cutoffs are scarce. Recently, Reed *et al.* compared different histologic cut-points for treatment response: whereas a threshold of <15 eos/hpf was attainable in most patients and identified patients with endoscopic improvement, a lower cut-off of <5 eos/hpf best predicted combined symptomatic and endoscopic response.[40] At present, the patients in clinical practice reaching histologic remission defined by <15 eos/hpf do not typically undergo therapeutic escalation to reach the target of ≤6 eos/hpf. However, a formal prospective blinded RCT examining the utility of different treatment targets is needed to answer the clinical

696 question of whether remission should be targeted at either <6 eos/hpf or <15 eos/hpf, and whether
697 maintenance of these treatment targets results in better outcomes for patients, including less
698 strictures and impactions. Multiple guidelines since 2007 have now established ≥15 eos/hpf as
699 the cutoff for diagnostic purposes, and the panel voted that the proportion of patients achieving a
700 PEC lower than this threshold should continue to be reported.[3, 41, 42] Finally, the panel identified
701 that a threshold of ≤ 6 eos/hpf may be too rigorous to achieve and may not necessarily be
702 appropriate for potential future drug targets with mechanisms of action that do not directly inhibit
703 eosinophils (*e.g.* anti-fibrotic therapies). Nevertheless, we anticipate that in future trials designed
704 for regulatory approval of medications, the proportion of patients with post-treatment PEC <15
705 eos/hpf and ≤6 eos/hpf will both be reported.
706
707 Finally, there was a discussion regarding the use of the EoEHSS as a measure of histologic
708 disease activity. The EoEHSS has been previously demonstrated to be valid, reliable, responsive,
709 applicable in adult and pediatric populations, correlates with other measures of disease activity
710 including patient symptoms, and measures histologic items that are prevalent in patients with EoE
711 beyond the PEC alone.[21, 22, 24, 43-46] For these reasons, panelists felt strongly that the EoEHSS
712 should be routinely evaluated in RCTs. However, panelists did not include the EoEHSS as a core
713 outcome in observational studies due to concerns about the time required for interpretation, the
714 complexity of the score, and lack of an atlas to help pathologists not specialized in EoE to score
715 some of the features.
716
717 There was consensus that endoscopic endpoints should be reported in all EoE studies, and that
718 the EREFS should be used to standardize endoscopic evaluation. The EREFS score has been
719 shown to accurately identify disease activity in both adult and pediatric populations[47], can be
720 reliably scored by experts and quickly learned by non-experts[18, 48], and is responsive to
721 treatment.[24, 49, 50] However, there was debate as to whether the EREFS should be scored on a 0-

9 or 0-8 scale (depending on the grading of linear furrows), recognizing that scoring on a broader range may improve the sensitivity of the instrument for detecting change post-treatment and can be converted to a 0-8 scale *post-hoc* if required. Although two-thirds of the ratification panel was in favor of reporting the EREFS using a 0-9 scale, the consensus on the 0-8 scale was included in the COS for methodologic consistency. Functionally, reporting individual component subscores of the EREFS and grading furrows on a 3-point rather than binary scale nullifies this dilemma, and is also required to discern endoscopic inflammatory vs. fibrostenotic disease activity.

Although both the DSQ and symptom-based EEsAI PRO (7-day recall period) instruments were recommended for use in RCTs of adults with EoE, there were concerns that US regulatory authorities have specifically recommended the use of an instrument with a 24-hour recall period. The DSQ was the only 24-hour recall instrument selected out of a myriad of options and is the first such instrument to be validated for use in RCTs, allowing assessment of endpoints such as dysphagia-free days.[14, 23, 37, 50, 51] Other instruments, including both conceptually similar and dissimilar tools, such as the Dysphagia Symptom Diary and Numeric Rating Scales for Dysphagia and Pain, respectively, have been used in other drug development programs, as historically licensing DSQ to all interested parties has not been possible.[14, 50] The use of different instruments in different clinical trials poses challenges for evidence synthesis and impedes cross-comparison between studies. Therefore, even though instruments such as EEsAI PRO do not use a 24-hour recall, they may continue to be used as secondary endpoints to allow for comparisons with existing data or when implementation of a daily electronic diary poses challenges for investigator-initiated studies. No specific instruments reached consensus for use in observational studies. This likely reflects the different logistical challenges and heterogeneity in observational trials, wherein daily or extensive assessments may not be feasible, and many of the instruments proposed remain proprietary.

747

748 The development of a generic daily recall instrument was identified as a priority, as existing tools
749 such as DSQ and episode-based instruments may be difficult or expensive to implement outside
750 of industry-sponsored RCTs. Whether such instruments should use broad language to describe
751 dysphagia is another relevant consideration and was a subject of much debate. Currently, most
752 available instruments do not assess all possible symptoms relevant for adults with EoE and do
753 not include the most common language used by patients to describe dysphagia (food being stuck,
754 delayed passage of food, tightness, and trouble swallowing based on qualitative work).[19, 51] "Food
755 being stuck" narrowly missed the consensus criteria during ratification round because there were
756 concerns raised that this more accurately reflected food bolus impaction rather than dysphagia,
757 although no clear distinction between language used to describe short- and long-lasting episodes
758 of dysphagia has been noted in qualitative work. Lastly, data on cross comparisons of instruments
759 are scarce, and it is not clear whether assessing symptoms more broadly by including all possible
760 dysphagia language as well as all symptom domains relevant to patients might explain to a greater
761 extent the variation in severity of biologic findings when compared to assessing dysphagia
762 frequency alone.[52, 53]

763

764 The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0) is the only currently
765 available instrument for assessing symptoms in pediatric patients with EoE. This tool was studied
766 and validated in pediatric patients ages 8 and older, as well as by parent-proxy in patients ages
767 2 and older. Although there are data to convincingly demonstrate the alignment between patient-
768 reported and proxy-reported symptom severity, there is not enough data to understand the
769 performance of this instrument in the context of treatment response, especially given that: 1) there
770 is a 30-day recall period for this instrument; 2) age influences symptom presentation in children,
771 often without true dysphagia; and 3) a broad range of symptoms needs to be assessed.[25, 54, 55]

772 Health-related QoL is frequently assessed in children with EoE using the PedsQoL. Health-related
773 QoL scores are associated with EoE symptom scores and improve following treatment.[56, 57] While
774 assessment of general health-related QoL allows for comparisons across other diseases, there
775 was debate about the utility of assessing general health-related QoL in pediatric patients rather
776 than disease-specific QoL leading to the exclusion of this measure from the COS.

777

778 Our study has several strengths. We used rigorous methods to develop this COS; each method
779 had unique strengths. For example, anonymous online Delphi surveys allowed us to capture a
780 large panel of international experts, whereas in-person live discussions highlighted more nuanced
781 arguments for or against specific outcomes. However, we also acknowledge some important
782 limitations. First, there are some outcomes included in the COS that appear to be inconsistent
783 (*e.g.* reporting both eos/hpf and eos/mm^2, reporting PEC<15 eos/hpf vs. ≤6 eos/hpf). This typically
784 reflects insufficient empirical evidence to guide decision making, and in these scenarios, we have
785 recommended both measures be reported. Nevertheless, we realize this recommendation does
786 not remove an ambiguity with respect to reporting of trial results especially with regards to
787 measures of spread, which are not easily converted between units. Collecting this data will
788 facilitate comparative analyses that can inform future iterations of the COS. Second, we restricted
789 the COS to measures of treatment efficacy or effectiveness, rather than safety outcomes. Given
790 the diverse drug targets under investigation, which have different safety profiles from conventional
791 corticosteroids and dietary therapies, it was felt that proscribing adverse event reporting was
792 outside the scope of this COS. Third, we engaged patients for deciding the outcome domains of
793 importance. However, patients were recruited from a single country and there was limited
794 racial/ethnic diversity. Nevertheless, almost all patients included in this study identified similar
795 outcome domains of importance, which made it unlikely that these would be dropped from later
796 rounds of the Delphi process. Additionally, specific patient input on measurement tools was not

sought because these decisions were primarily based on technical factors. For example, while we felt it was critical to assess patient perceptions of endoscopic evaluation as an outcome, the specific considerations regarding whether the EREFS should be scored on a 0-8 vs. 0-9 scale were less relevant for patients. Fourth, some domains, such as patients' perception of health or secondary impact on caregivers, were likely voted as subjects of future research by the experts, because of limited data currently available in these areas. Fifth, we recognize that we included authors who have been pivotal in developing instruments that are advocated for in this COS. However, we felt it was important to capture the expertise of the global EoE community. Finally, we did not engage industry stakeholders as this was an academic exercise, and did not engage regulators as they generally precluded from these types of initiatives due to potential conflicts of interest.

In conclusion, we have developed an internationally guided COS for use in pharmacologic and dietary therapeutic trials in pediatric and adult patients with EoE. Groups assessing EoE therapies should be encouraged to adopt this COS to reduce the heterogeneity in outcome reporting and improve comparability to future studies. We recognize that the endpoints used in EoE trials have evolved rapidly over the past two decades. While this is the first iteration of a COS in EoE, we anticipate that ongoing work in the development and validation of new instruments for measuring disease activity will shape both future versions of this COS and the field moving forwards.

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1002 **TABLES**

1003 **Table 1.** Expert panel demographic characteristics.

	Outcome Domains n=66	Delphi Round 1 Survey n=69	Delphi Round 2 Survey n=62	Ratification Meeting n=27
Specialty, n (%)				
Gastroenterology	33 (50.0)	38 (55.1)	35 (56.5)	16 (59.3)
Allergy	16 (24.2)	14 (20.3)	12 (19.4)	2 (7.4)
Pathology	11 (16.7)	10 (14.5)	8 (12.9)	5 (18.5)
Other	6 (9.1)	7 (10.1)	7 (11.3)	4 (14.8)
Patient Population, n (%)				
Adult only (≥18 years)	31 (47.0)	32 (46.4)	31 (50.0)	13 (48.1)
Both adult and pediatric	17 (25.8)	19 (27.5)	18 (29.0)	7 (25.9)
Pediatric only (<18 years)	18 (27.3)	18 (26.1)	13 (21.0)	7 (25.9)
Practice Setting, n (%)				
Academic Hospital/Clinic	58 (87.9)	60 (87.0)	54 (87.1)	23 (85.2)
Non-Academic Hospital/Clinic	8 (12.1)	9 (13.0)	8 (12.9)	4 (14.8)
Geographic Region, n (%)				
United States	37 (56.1)	40 (58.0)	35 (56.5)	15 (55.6)
Europe	25 (37.9)	24 (34.8)	23 (37.1)	8 (29.6)
Other	4 (6.1)	5 (7.2)	4 (6.5)	4 (14.8)

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Table 2. Voting distribution on a 9-point Likert scale for the importance of different outcome domains for inclusion in a core outcome set for eosinophilic esophagitis.

Outcome Domain	Not important for inclusion (1-3)	Important but not critical for inclusion (4-6)	Critical for inclusion (7-9)
Histology	0 (0%)	2 (3.0%)	65 (97.0%)
Endoscopy	1 (1.5%)	3 (4.6%)	61 (93.8%)
Patient-reported symptoms	0 (0%)	6 (9.1%)	60 (90.9%)
EoE-specific quality of life	1 (1.6%)	15 (23.4%)	48 (75.0%)
Biomarkers	6 (9.2%)	30 (46.2%)	29 (44.6%)
Esophageal distensibility	3 (4.9%)	33 (54.1%)	25 (41.0%)
Genetic profiling	19 (29.7%)	28 (43.8%)	17 (26.6%)
Immunologic dissection	14 (21.2%)	37 (56.1%)	15 (22.7%)
Patient perception of health	1 (1.6%)	34 (53.1%)	29 (45.3%)
Secondary impact on caregivers	10 (15.6%)	39 (60.9%)	15 (23.4%)
Resource utilization	14 (23.7%)	33 (55.9%)	12 (20.3%)

Table 3. Core outcome set for eosinophilic esophagitis.

Outcome Domain	Randomized Controlled Trials	Observational Studies
Histopathology	□ Peak esophageal eosinophilia (and appropriate measures of spread, such as error terms or confidence intervals) should be measured and reported in all RCTs, expressed as: ▪ Number of eosinophils per high-power field (400 × magnification) ▪ Number of cells adjusted per mm^2 (400 × magnification)	□ Peak esophageal eosinophilia (and appropriate measures of spread, such as error terms or confidence intervals) should be measured and reported in all observational studies, expressed as: ▪ Number of eosinophils per high-power field (400 × magnification) ▪ Number of cells adjusted per mm2 (400 × magnification)
	□ Histologic remission should be measured in all RCTs ▪ In RCTs, histologic remission should be defined based on a peak eosinophil count of < 15 esophageal eosinophils per high-power field in any location [a]	□ Histologic remission should be measured in all observational studies ▪ In observational studies, histologic remission should be defined based on a peak eosinophil count of < 15 esophageal eosinophils per high-power field in any location
	□ The grade (severity) and stage (extent) of all components in the EoE Histologic Scoring System (EoEHSS) should be measured and reported in all RCTs ▪ The EoEHSS remission score should be measured and reported in all RCTs: for each item, proximal and distal esophagus: remission score of ≤ 3 for grade AND ≤ 3 for stage AND peak eosinophil count of < 15 eos/hpf	
Endoscopy	□ The Endoscopic Reference Score (EREFS) should be measured and reported in all RCTs ▪ The EREFS should be scored from 0 to 8, scoring the most severe grade of esophageal EoE-associated features present in the proximal and distal esophagus (with furrows scored as absent or present) [b]	□ The Endoscopic Reference Score (EREFS) should be measured and reported in all observational studies ▪ The EREFS should be scored from 0 to 8, scoring the most severe grade of esophageal EoE-associated features present in the proximal and distal esophagus (with furrows scored as absent or present) *
	□ Endoscopic remission based on EREFS should be measured and reported in all RCTs and observational studies ▪ In RCTs or observational studies, the endoscopic EREFS-based remission should be defined as an EREFS score ≤ 2 (based on EREFS scoring from 0 to 8[b] ▪ In RCTs or observational studies, endoscopic inflammatory EREFS-based remission should be defined as the inflammation-associated components (exudate, edema, furrows) score ≤ 2 (based on EREFS scoring from 0 to 8) [c] ▪ In RCTs or observational studies, the endoscopic fibrotic EREFS-based remission should be defined as categorical definition as absence of strictures, moderate and severe rings	

Outcome Domain	Randomized Controlled Trials	Observational Studies
Patient-Reported Symptoms	□ In all RCTs, symptom severity in adults with EoE should be assessed using a generic instrument with a daily recall period [d] □ In all RCTs, symptom severity in adults with EoE should be assessed using the following instruments: ▪ Dysphagia Symptom Questionnaire ▪ Eosinophilic Esophagitis Activity Index (7-day recall period) □ In all RCTs, the following language should be used to query dysphagia in adults with EoE: ▪ Dysphagia defined as trouble swallowing ▪ Dysphagia defined as delayed or slow passage of food □ In all RCTs, symptom severity in pediatric EoE patients should be measured using Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0)	No patient-reported symptom instruments met consensus thresholds for use in all observational studies □ In all observational studies, the following language should be used to query dysphagia in adults with EoE: ▪ Dysphagia defined as trouble swallowing ▪ Dysphagia defined as delayed or slow passage of food
Quality of Life	□ In all RCTs, EoE-specific quality of life in adults should be measured using EoE Quality of Life (EoE-QoL-A) questionnaire □ In all RCTs, pediatric EoE-specific quality of life should be measured using The Pediatric Quality of Life Inventory (PedsQL) EoE Module ▪ When using PedsQL EoE Module for children, for whom both parent-proxy report and child self-report are available, both should be reported in all RCTs	No patient-reported quality of life instruments met consensus thresholds for use in all observational studies

[a] Remission cut-off of <15 eosinophils/hpf corresponding to <60 eosinophils/mm^2

[b] See text (COS: Endoscopy Outcomes) for full details; if the EREFS is scored from 0 to 9, recommended to report component scores to calculate post-hoc an EREFS score on a 0 to 8 scale

[c] Endoscopic remission recommended to be defined by EREFS≤2 if scored on 0 to 8, or 0 to 9 scale

[d] See text (COS: Patient-Reported Symptoms) for full details; considered appropriate to use a generic instrument with a daily recall period in accordance with regulatory recommendations

Abbreviations: EoE eosinophilic esophagitis; EoEHSS EoE Histologic Scoring System; EoE-QoL-A, EoE Quality of Life for adults, EREFS Endoscopic Reference Score; hpf high power field; PedsQL Pediatric Quality of Life Inventory; PEESS Pediatric EoE Symptom Score; RCT randomized controlled trial.

FIGURE LEGENDS

Figure 1. Core outcome set development process.

Figure 2. Outcome domains for inclusion in the eosinophilic esophagitis core outcome set.

Figure 1

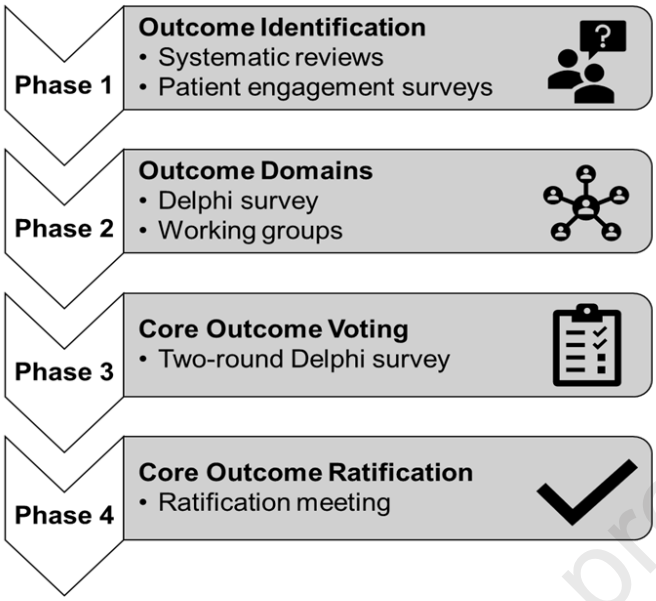

Figure 2