Development of a Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis (COREOS): An International Multidisciplinary Consensus

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COMMENTARY

The Need to Define Consensus Outcomes in Eosinophilic Esophagitis

There has been tremendous interest in developing eosinophilic esophagitis (EoE)-specific pharmacotherapies,[1] and over 50 active or enrolling interventional studies are currently registered on Clinicaltrials.gov. 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.[2-5] Despite these breakthroughs, efficient drug development in EoE has been hampered by the lack of standardized outcome measures that can be used in both registrational trials to support labelling claims and in observational studies to answer practice-based questions. 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.[6] Given the lack of consensus and the increasing scrutiny of 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.[7] Using a COS to inform study design and choose endpoints can improve the efficiency of clinical studies by ensuring appropriate outcomes are measured, minimize heterogeneity in reporting, reduce the risk of publication bias, and improve the quality of evidence synthesis by 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 the Eosinophil Gastrointestinal Disorders (EGID) Committee of The American Academy of Allergy, Asthma, and Immunology (AAAAI), we developed an international consensus COS for

use in studies of pharmacologic and dietary interventions for adult and pediatric patients with EoE (COREOS).

Methods for Defining the COS

Detailed methods used to define the COS are summarized in the accompanying Meeting Summary. We used a multiple phase approach, conducted in accordance with recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) initiative[7, 8] to identify relevant outcome domains and endpoint definitions for randomized controlled trials (RCTs) and observational studies in adult and pediatric patients with EoE. First, a series of systematic reviews[6, 9] and patient engagement surveys[10] were conducted to identify candidate outcomes of importance. Input was gathered from a diverse range of patients with EoE to determine their values on the importance of different outcomes and recruited using purposive sampling from multiple clinics to capture a range of disease duration, disease activity, and treatment experiences. A total of 36 patients with EoE participated in semi-structured interviews and 109 patients with EoE completed a paper-based survey. Outcomes identified in the patient engagement surveys and through systematic literature reviewer were organized into eleven domains, and a series of working group meetings were held to review the pertinent endpoints. These domains were then discussed in a moderated face-to-face meeting at Digestive Disease Week 2019 (San Diego, United States) and a Delphi panel of multidisciplinary experts voted to categorize these into core, important, and research agenda domains based on the Outcome Measures in Rheumatology (OMERACT) model.[11] In phase 3, a comprehensive list of outcome measures within each core domain was evaluated in a two-round Delphi survey to establish consensus. Finally, a virtual ratification meeting was held to vote on the final outcomes included in the COS.

The COS panel included diverse stakeholders, reflecting a broad range of clinical knowledge and geographical diversity, including patients with EoE, gastroenterologists, pathologists, allergists, dieticians, psychologists, researchers, and methodologists. Several rounds of Delphi surveys were completed to first rank each domain and subsequently individual outcomes on a 9-point Likert scale.[12] Scores of 1-3 indicate an outcome domain 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. Outcome domains and outcome definitions scored in the 7-9 range by ≥70% of panelists and in the 1-3 range by <15% of panelists were considered to have met consensus. A moderated video conference to ratify the final COS was conducted December 8, 2020. Although this was initially planned as a face-to-face meeting, this was amended to a virtual conference due to COVID-19 public health restrictions. After discussion, panelists anonymously voted on the final items as "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.

A COS for EoE

Four outcome domains were voted as critical for inclusion in an EoE COS: *histopathology, endoscopy, patient-reported symptoms,* and *EoE-specific quality of life (QoL)* (**Figure 1**). While endpoints such as genetic profiling, biomarkers, esophageal distensibility, patient perceptions of health, and immunologic endpoints were important, they were not deemed critical for assessment in every study at this time. Patients with EoE identified improvement in EoE-related symptoms and QoL as the most important outcome domains: >90% of patients identified improvements in these domains as important in both the short and long-term. From the four core domains, a total of 122 outcome definitions were identified. Over two rounds of Delphi survey voting by 69 (Round 1) and 62 (Round 2) panelists, a total of 59 outcomes were

354 considered for inclusion (18 for histology, 12 for endoscopy, 19 for patient-reported symptoms,
355 and 10 for EoE-specific QoL). At the ratification meeting, 42 items were discussed and voted on
356 with 33 items included in the final COS. These are summarized in **Table 1**.
357
358 **COS: Histopathology Outcomes**
359 There was consensus that the peak eosinophil count (PEC) should be reported in all RCTs and
360 observational studies, expressed either as eosinophils (eos) per high power field (hpf) (including
361 exact area used and the hpf size reported in mm^2) or as eos per mm^2, viewed at 400 ×
362 magnification. Several panelists identified that both measures should be reported, as eos/hpf
363 has been historically used, whereas eos per mm^2 adjusts for differences in microscope ocular
364 field size. In RCTs, the EoE Histology Scoring System (EoEHSS)[13] should be used, and both
365 the grade and stage of each component item reported. There was consensus that histologic
366 remission should be reported in all studies, although the precise threshold for histologic
367 remission was debated. The proportion of patients with < 15 eos/hpf in all esophageal locations
368 should be reported, but there was disagreement on reporting a more stringent threshold of ≤ 6
369 eos/hpf.
370
371 *Implications and Future Directions:* Given the importance of eosinophilic inflammation in
372 defining EoE, histopathology was almost universally agreed upon as a core domain. However,
373 three areas of controversy garnered discussion. First, although using eos/mm^2 was felt to be
374 advantageous for standardizing density measurements across different microscopes and field
375 sizes,[14] most of the literature to date has expressed the PEC per hpf. There was consensus that
376 this should continue to be reported to facilitate historical treatment comparisons although we
377 advocate for a greater emphasis on reporting eos/mm^2 (using remission definitions of PEC ≤25
378 eos/mm^2 and <60 eos/mm^2, corresponding to PEC of ≤6 eos/hpf and <15 eos/hpf, respectively).
379 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 recent recommendations from the United States Food and Drug Administration (US FDA).[15] Multiple guidelines have established ≥15 eos/hpf as the cutoff for diagnostic purposes, and the panel voted that the proportion of patients achieving a PEC lower than this threshold should continue to be reported.[16-18] A threshold of ≤ 6 eos/hpf may be too stringent to achieve and may not necessarily be appropriate for potential future drug targets with mechanisms of action that do not directly inhibit eosinophils. Nevertheless, we anticipate that in future trials designed for regulatory approval of medications, the proportion of patients with post-treatment PEC <15 eos/hpf and ≤6 eos/hpf will both be reported. Finally, the EoEHSS has been previously demonstrated to be valid, reliable, responsive, applicable in adult and pediatric populations, and measures histologic items that are prevalent in patients with EoE beyond the PEC alone.[13, 19, 20] For these reasons, panelists felt strongly that the EoEHSS should be routinely evaluated in RCTs. However, the EoEHSS was not included as a core outcome in observational studies due to concerns about the time required for interpretation and lack of an atlas to help pathologists not specialized in EoE to score some of the features, although uptake in clinical practice may increase as it is adopted in RCTs.

COS: Endoscopic Outcomes

The panel voted that the EoE Endoscopic Reference Score (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. Different versions of the EREFS were explored (scoring from 0-8, 0-9, 0-16, and 0-18 with alternative definitions or weighting of the EREFS components). There was consensus to score the major features of the EREFS from 0-8 with furrows assessed as absent/present; 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, when compared to scoring the furrows ordinally using grade 0 (absent), grade 1 (mild, vertical lines without visible depth), and grade 2 (severe, vertical lines with mucosal depth/indentation). 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. For both RCTs and observational studies, there was consensus that endoscopic remission should be defined using an EREFS ≤ 2.

Implications and Future Directions: The EREFS score has been shown to accurately identify disease activity in both adult and pediatric populations, can be reliably scored by experts and quickly learned by non-experts, and is responsive to treatment.[21-23] From this consensus, we recommend scoring the EREFS in all EoE RCTs and observational studies, reporting individual component items, and using a cutoff of ≤ 2 for endoscopic remission. However, there was debate as to whether the EREFS should be scored on a 0-9 or 0-8 scale, recognizing that scoring on a broader range may improve the sensitivity of the instrument for detecting change in an RCT setting and can be converted to a 0-8 scale *post-hoc* if required. Functionally, reporting individual component subscores of the EREFS is also required to discern endoscopic inflammatory versus fibrostenotic disease activity. Investigators may choose to grade furrows on a 3-point rather than binary scale and collapse in post-hoc analyses if required.

COS: Patient-Reported Symptoms and Quality of Life

There was consensus that validated instruments for patient-reported symptoms, including the Dysphagia Symptoms Questionnaire (DSQ) and the symptom-based EoE Activity Index (EEsAI) with 7-day recall period, should be assessed in EoE RCTs. There was discussion that guidance from the US FDA highlights the use of clinical outcome assessment instruments that use daily evaluations. The EEsAI was developed and has been used in previous RCTs with a 7-day recall period as secondary endpoint, and this outcome was voted to be included in the COS.

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. 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. Given the multitude of instruments with daily recall currently used in RCTs, EEsAI 7-day recall period may be used as secondary endpoint to allow for cross-comparisons between existing instruments.

There was also consensus that the language used to query dysphagia in adults with EoE include trouble swallowing and delayed/slow passage of food. “Food being stuck” did not reach consensus thresholds in the ratification round. 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.

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 concluded that disease specific QoL measures rather than generic QoL measures should be chosen for this domain. No instruments for use in all observational studies met the consensus threshold for inclusion in the COS.

458 *Implications and Future Directions:* The development of a generic daily recall instrument was
459 identified as a priority, as existing tools such as DSQ and episode-based instruments may be
460 difficult or expensive to implement outside of industry-sponsored RCTs. Whether such
461 instruments should use broad language to describe dysphagia is another relevant consideration,
462 because most available instruments do not assess all possible symptoms relevant for adults
463 with EoE or do not include the most common language used by patients to describe
464 dysphagia.[24, 25] "Food being stuck" narrowly missed the consensus criteria during ratification
465 round because there were concerns raised that this more accurately reflected food bolus
466 impaction rather than dysphagia, although no clear distinction between language used to
467 describe short- and long-lasting episodes of dysphagia has been noted in qualitative work.
468 Lastly, data on cross comparisons of instruments are scarce, and it is not clear whether
469 assessing symptoms more broadly by including all possible dysphagia language as well as all
470 symptom domains relevant to patients might explain a greater extent of the variation in severity
471 of biologic findings when compared to assessing dysphagia frequency alone.
472
473 The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0) is the only currently
474 available instrument for assessing symptoms in pediatric patients with EoE. Although there are
475 data to convincingly demonstrate the alignment between patient-reported and proxy-reported
476 symptom severity, there are not enough data to understand the performance of this instrument
477 in the context of treatment response, especially given that: 1) there is a 30-day recall period for
478 this instrument; 2) age influences symptom presentation in children; and 3) a broad range of
479 symptoms need to be assessed.
480
481 **Conclusions**
482 In conclusion, we have developed an internationally guided multidisciplinary COS for use in
483 therapeutic trials in pediatric and adult patients with EoE. Groups assessing EoE therapies

should be encouraged to adopt this COS to reduce 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. Indeed, limitations of existing instruments for measuring histology, endoscopy, symptoms, and quality of life were highlighted during the discussions that occurred in the consensus process and are reviewed in the accompanying Meeting Summary. Therefore, while this is the first iteration of a COS in EoE, we anticipate that ongoing work in the development of new instruments for measuring disease activity will shape the field moving forwards. Importantly, the development of this COS represents only the minimum outcomes that should be currently measured but should not discourage the development and validation of potentially more robust or appropriate instruments to measure disease activity in the future. In fact, we urge all investigators to measure other potential outcomes of interest, in addition to these benchmarked minimum endpoints. Areas of research priority, including comparisons of the performance characteristics of different tools for measuring disease activity in diverse patient populations, will help to inform the next version of this COS.

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572 **Tables and Figures Legend**

573

574 **Table 1.** Core outcome set for eosinophilic esophagitis

575 **Figure 1.** Outcome domains for inclusion in the eosinophilic esophagitis core outcome set

576

577 **Table 1.** 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 major features of 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 major features of 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 with furrows graded as grade 0 (absent), grade 1 (mild, vertical lines without visible depth), and grade 2 (severe, vertical lines with mucosal depth), 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