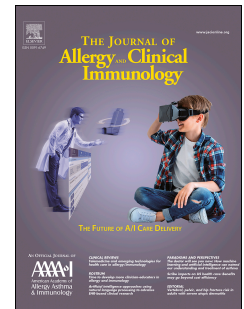


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The importance of using core outcome measures during therapeutic studies of eosinophilic esophagitis

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A clinical trial is only as good as its design, and an essential component of good study design is the selection of outcome measures that effectively address the trial question while advancing the field as a whole. Ideally, outcomes should be clinically relevant, easily interpretable, and sensitive to the effects of the study intervention.¹ There are also practical and cost-related factors, as well as value in selecting outcomes that are objective or can be measured in a minimally biased manner. While a single study in isolation could choose successful outcomes by subscribing to these parameters alone, there are additional considerations when designing a study to be comparable to others in the field. For example, even seemingly insignificant differences in measured outcomes can make the comparison or synthesis of evidence across trials difficult or even impossible. Non-uniform outcome reporting can also lead to outcome reporting bias—when authors selectively report outcomes to increase the perceived impact of the trial.² To facilitate the adoption of uniform outcomes that are comparable across studies, there has been recent focus on developing core outcomes sets (COS) that represent the minimum outcomes that should be measured and reported by all trials of a specific condition.³ These COS, built with the input of multiple stakeholder groups, are designed to increase trial consistency, facilitate cross-trial synthesis, and ultimately expand the experimental utility of trials and expedite the delivery of effective therapeutics to clinicians and patients.

Eosinophilic esophagitis (EoE) is a form of chronic food allergy that affects 1 in 1,000 people in Europe and North America and has an incidence that is increasing by 12-17% per year.⁴ The symptoms of EoE are diverse and range from painful swallowing and malnutrition in infants and children to esophageal dysfunction and food impactions in adolescents and adults.⁵ A lack of targeted therapeutics for this condition, coupled with an expansion of our understanding of EoE immunopathology,⁶ has fueled a record number of EoE-related interventional trials with no less than 35 such studies currently planned or underway world-wide. Though several validated, reliable, and responsive instruments of EoE disease activity and symptomatology exist, there is no current consensus on a minimum set of outcome measurements that should be followed in

clinical trials. As a result, studies to date have reported heterogeneous outcome measures that have hindered trial interpretation and comparison.⁷

In this issue of JACI, Dr. Christopher Ma and a collection of EoE experts from across the globe report a COS for therapeutic studies of EoE (COREOS).⁸ The COREOS outcomes were developed for controlled and observational studies via a four-phase development process that included outcome identification via systemic review and patient engagement, outcome aggregation into domains via Delphi surveys and working groups, a voting phase where participants were asked to rank each outcome in two rounds, and ultimately an outcome ratification meeting. Through this process, the authors identified outcomes that spanned four domains: histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life (**Figure 1**).

In the histopathology outcome domain, the peak eosinophil count (via both the conventional eosinophils/high power field *and* eosinophils per mm² when viewed at 400x magnification) and histologic remission (at minimum the proportion of patients with <15 eos/hpf in all esophageal locations) was included for both randomized controlled trials (RCTs) and observational studies. The EoE Histology Scoring System was included for RCTs only. In the endoscopy outcome domain, the EoE Endoscopic Reference Score (both inflammatory and fibrotic) and endoscopic remission (defined as an EREFS score ≤2) were included for both randomized controlled trials (RCTs) and observational studies. In the patient-reported symptom domain, both the Dysphagia Symptoms Questionnaire and Eosinophilic Esophagitis Activity Index were recommended for RCTs only. Similarly, in the quality of life domain, the EoE-specific QoL questionnaire (for adults) and the Pediatric Quality of Life Inventory (for children) were recommended for RCTs only. Neither the patient-reported symptom domain nor the quality of life domain had specific recommendations for observational studies.

The strengths of the COREOS outcomes are many. Firstly, they represent a multinational and multidisciplinary effort to synthesize relevant scientific evidence, expert opinion, and patient experience into a unified set of core outcome measures. In doing so, they

incorporate historical and highly clinically relevant disease measures with validated instruments to standardize the measurement and reporting of more subtle aspects of EoE disease activity and symptomatology. There are also some limitations that will need to be addressed in future versions of the COREOS outcomes. For example, there was lack of consensus regarding instruments for measuring symptom severity or quality of life for observational studies. This is likely due to the degree of heterogeneity in the types and conduct of observational studies that make daily or extensive assessments infeasible and therefore recommending any one universal instrument difficult. However, this gap also provides opportunities for the development of new tools, such as a generic daily recall instrument, that are not proprietary and are better designed for select observational studies. In addition, there is still debate as to the best definition(s) of histologic remission in EoE, and in particular between the COREOS definition of <15 eos/hpf and the NIH regulatory guidance of <6 eos/hpf. The collection of additional data on the relationship between histologic inflammation, symptomatology, and EoE outcomes over the course of future trials will surely inform and help to refine this definition in future iterations of the COREOS exercise. Despite these limitations, the COREOS outcomes represent an important step forward that will help to standardize future EoE trials, facilitate meaningful treatment comparisons, improve the quality of data synthesis, and ultimately accelerate the identification of specific treatments for this important disease.

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Figure Legend(s):

Figure 1. The COREOS outcome domains: histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life.

Abbreviations:

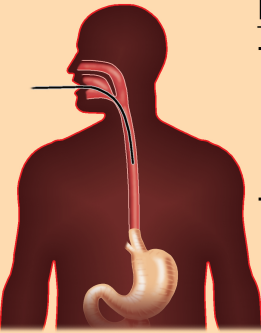
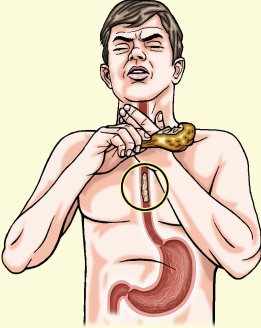
RCT C Randomized Controlled Trial

Eos - Eosinophils

Hpf C High-powered field

EREFS - Endoscopic Reference Score

PEESS - Pediatric Eosinophilic Esophagitis Symptom Scores

Histopathology  <u>RCTs & Observational:</u> -Peak Eosinophil Count (eos/hpf, eos/mm²) -Histologic Remission (% with <15 eos/hpf) <u>RCTs only:</u> -EoE Histologic Scoring System (grade & stage)	Endoscopy  <u>RCTs & Observational:</u> -EoE Endoscopic Reference Score (inflammatory & fibrotic) -Endoscopic Remission (EREFS ≤ 2, of 0 to 8 score)
Patient-Reported Symptoms  <u>RCTs only:</u> -Dysphagia Symptoms Questionnaire -Esophagitis Activity Index -PEESS (children) <u>Observational:</u> -None	EoE-Specific Quality of Life  <u>RCTs only:</u> -EoE-specific QoL questionnaire -Pediatric Quality of life Inventory (children) <u>Observational:</u> -None