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Heterogeneity in Crohn's Disease and Ulcerative Colitis Clinical Endpoints Leading to Uncertainties in the Real-World Setting

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Introduction & Objectives

Disease activity in Crohn's disease and ulcerative colitis may be assessed from symptoms, physical signs and laboratory, endoscopic or radiological measures of inflammation[1]. Clinical trials have traditionally used physician-reported composite outcome measures[2] to measure disease improvements or progression[3]. These 'activity indices' combine symptoms, signs and some objective parameters, such as the Crohn's Disease Activity Index (CDAI) or Mayo Clinic Score[1]. However, the choice of index definition varies across trials creating differential definitions for similar terms. Furthermore, the requirement for objective test results makes such instruments impractical for routine use at every clinical encounter and translation to the real-world setting[1]. Heterogeneity in clinical outcome measurement between real-world practice and clinical trials in Crohn's disease (CD) and ulcerative colitis (UC) makes comparisons across these settings challenging[3].

To better understand the similarities and differences in CD and UC clinical endpoints across real-world evidence (RWE) studies and randomised clinical trials (RCTs), we conducted a targeted litera ure review to collate clinical outcomes, aiming to better design future research.

Methods

- A targeted literature review was performed in MEDLINE and EMBASE to identify RCTs and RWE studies including more than 50 patients with CD and UC, published between January 2019 and May 2024. Duplicate studies were removed from the search results (**Figure 1**).
- One independent reviewer screened the results using the Population, Intervention, Comparison, Outcomes and Study design criteria (**Table 1**).
- Data on study design, clinical outcomes and disease specific measures were extracted.

Figure 1. Study flow diagram

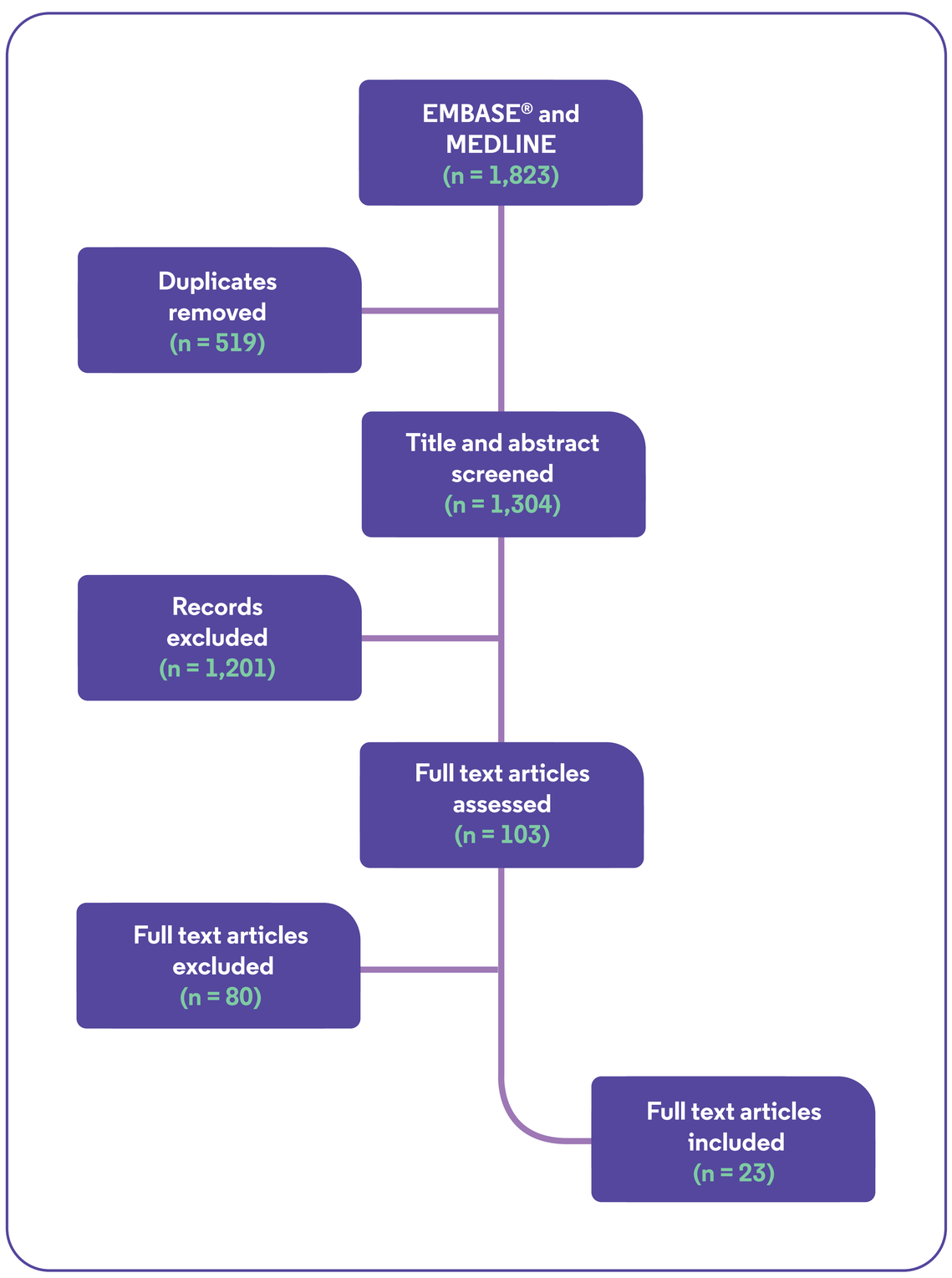

Table 1: PICOS criteria

PICOS item	Inclusion criteria
Population	Adults with Crohn's disease or ulcerative colitis
Intervention	Any pharmaceutical
Comparison	Pharmaceutical
Outcomes	All clinical outcomes measure
Study design	Randomised clinical trials Observational studies

Results

- Of 1,304 studies identified, 103 (54 RCTs; 49 RWE studies) were selected for full-text review. The most common clinical endpoints were remission and response.
- From the RCTs, we identified 18 unique definitions of clinical remission or response and 12 definitions for loss of response. Clinical remission and response in RCTs for UC were primarily defined by the MCS, with minor differences in score cut-offs. For CD, the definition of remission varied significantly, including the use of CDAI and average daily stool frequency (SF).
- Among the RWE studies, aside from MCS and CDAI, remission and response were typically defined by the Harvey Bradshaw Index (HBI) and Simple Clinical Colitis Activity Index (SCCAI).
- Disease activity-related events were also collected as the primary clinical endpoints in RWE studies; these included hospitalisation, disease-related surgeries and change of therapy. Differences in score cut-offs were observed within and across study designs.

Table 2. Efficacy outcome domains and measurement tools

Outcome Domain	Primary or secondary outcomes	Measurement scores/indices
Clinical or composite clinical outcomes	• **Clinical response** • **Clinical remission** • Corticosteroid-free response/ remission • Sustained response/remission • Combined clinical and endoscopic response/remission • Partial/complete response • Disease relapse or worsening	• **Ulcerative Colitis Disease Activity Index (UCDAI)** • Sutherland Disease Activity Index • **Mayo Clinic Score** • **Modified Mayo Clinic Disease Activity Index** • **Physician Global Assessment** • Rachmilewitz Clinical Activity Index • Modified Truelove and Witt Criteria • Ulcerative Colitis Scoring System • Ulcerative Colitis Clinical Score • **Harvey Bradshaw Index**
Endoscopic outcomes	• **Endoscopic response** • **Endoscopic remission** • Endoscopic mucosal healing	• **Ulcerative Colitis Disease Activity Index (mucosal appearance subscore) and Modified UCDAI endoscopy subscore for mucosal friability** • Sutherland Disease Activity Index (mucosal appearance subscore) • Mayo Clinic Score (endoscopic appearance subscore) • Baron and Modified Baron Score • **Simple Endoscopic Score**
Histologic outcomes	• Histologic response • Histologic remission	• Tissue drug concentrations • Tissue cytokine, leukocyte, receptor, or gene expression • Geboes Score Riley Score • Modified Riley Score • Saverymuttu Criteria

Note: Items listed in bold are used in both real world data studies and randomized clinical trials **Abbreviations**: UCDAI: Ulcerative Colitis Disease Activity Index

Conclusion

In conclusion, this research in Crohn's disease and ulcerative colitis has shown there is an inclination towards the reporting of clinical, endoscopic, histologic, biomarker, and patient-reported endpoints in clinical trials. However, the heterogeneity of outcome definitions as well as the evolving landscape of treatment endpoints highlights the need for an international consensus on core outcomes for use in future trials. This is important to facilitate both direct and indirect comparisons of treatment efficacy between the clinical trial and real-world setting.

Presented at ISPOR Europe 2024, Barcelona, Spain | November 17-20 2024

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Acknowledgments and Disclosures:
HS, XQ, WS, IA, BB, BO and MR are all employees of Clarivate. The study has been funded by Clarivate.