A Systematic Review of Outcomes and Adverse Events for Randomised Controlled Trials in Crohn's Disease

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Background and objectives

Randomised controlled trials in Crohn's disease have evolved over time since 1972 with a variety of study designs, and assessment of disease activity and treatment response[1]. The introduction of biologic therapies has revolutionised therapy for patients with Crohn's disease and has heralded a new approach to measuring response, which has challenged the suitability of traditional disease activity indices as primary end-points, particularly the Crohn's Disease Activity Index (CDAI)[2]. There has been increased interest in the use of objective measures of inflammation, such as biomarkers and endoscopic lesions, and patient reported outcomes as combination trial endpoints.

Despite major progress in drug development for Crohn's disease (CD) and advances in trial methodology, there is no internationally recognised minimum set of standardised outcomes to be measured and reported in all trials, known as a core outcome set (COS)[3]. Poor standardisation in outcome reporting may impact negatively on translation of trials into practice, affecting decision making at both regulatory and clinical levels.

We undertook a systematic review to explore heterogeneity and time trends in the reporting of efficacy and safety outcomes in placebo-controlled randomized controlled trials (RCTs) of patients with CD.

Methods

We searched MEDLINE, EMBASE, CINAHL and Cochrane Library from their inception to November 2015, for RCTs of adult CD patients with treated with medical or surgical therapies. We extracted information on efficacy and safety outcomes, definitions of end-points, and measurement instruments.

Analysis of the efficacy outcomes focused on the primary and secondary outcomes recorded in the papers. Safety- related outcomes analysis did the same but also included analysis of all reported adverse events data and study withdrawals. Adverse events reporting was considered at two levels of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy: system organ classification (SOC) and higher level group term (HLGT), the latter of which is considered a clinically relevant grouping of preferred terms (PTs) for low level signs and symptoms[4].

A secondary analysis considered the reporting of outcomes that were not specified as primary or secondary endpoints. To explore temporal trends studies were stratified by publication date (pre-2009 and 2009-onwards).

We reported the study according to PRISMA guidance[5,6], which is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

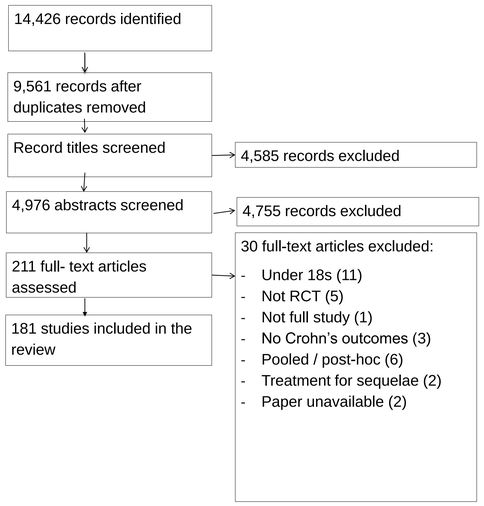
Results

9,561 studies were identified in the review and 181 RCTs were included in the review (figure 1) comprising 23,850 patients. Induction of remission was the focus of 110 trials (60.8%), 104 medical and 6 surgical interventions. Maintenance of remission was the focus of 71 trials (39.2%). Biologics were the intervention of interest as in 33.7% of studies, as either monotherapy or part of a combination therapy.

92.3% of trials reported clinical efficacy outcomes as a primary or secondary endpoint, which was consistent across the time periods (Figure 2). CDAI was the dominant index, used to measure primary and secondary endpoints in 77.9% of studies and to determine clinical response or remission in 63.5% of trials. However, there was heterogeneity, with 35 definitions of response or remission. CDAI<150 was the commonest endpoint, but reporting reduced between periods (46.4% to 41.1% of trials), whilst CDAI100 reporting increased (16.8% to 30.4%).

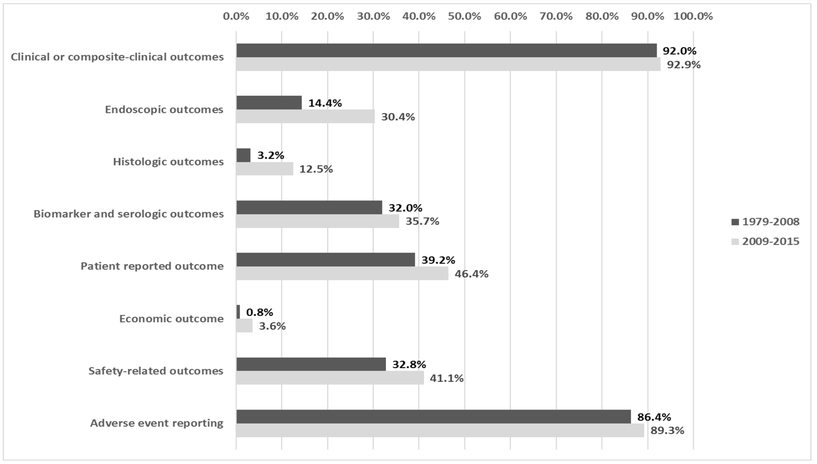
Reporting of objective measures of inflammation increased over time, but with lack of standardisation. Reporting of both histologic and endoscopic outcomes increased, from 3.2% to 12.5% and from 14.4% to 30.4% of RCTs, respectively. Biomarker reporting increased from 33.3% to 40.6% of trials. Patient-reported outcome measures (PROMs) were reported in 41.4% of trials with growth in reporting from 39.2% to 46.4%.

Figure 1: PRISMA flow diagram



Results

Figure 2: Proportion of Crohn's Disease RCTs reporting key primary and secondary efficacy and safety outcomes, stratified by year of publication into pre-2009 and 2009 onwards



Safety outcomes were reported explicitly as primary or secondary outcomes in 35.4% of trials and reporting increased from 32.8% to 41.1% between the time periods (Figure 2). The most common trial endpoints were the overall rate of adverse events.

Adverse event reporting increased from 86.4% to 89.3% over the time period. The ten most commonly reported HLGTs are shown in Table 1. Gastrointestinal signs and symptoms were reported in 65.2% of RCTs, including events such as nausea, vomiting and abdominal pain. Infections, including abscesses and opportunistic infections, were reported by more than half of studies, as were headaches.

Table 1: Most commonly reported adverse events by MedDRA Higher Level Group Terms (HLGT)

System Organ Classification	Higher Level Group Term	Studies reporting n (%)		Example preferred terms
Gastrointestinal disorders SOC	Gastrointestinal signs and symptoms	118	65.2%	Nausea, vomiting, abdominal pain, flatulence, abdominal distention
Infections and infestations SOC	Infections - pathogen unspecified	95	52.5%	Abscess, infection, opportunistic infection, respiratory tract infection, nasopharyngitis
Nervous system disorders SOC	Headaches	91	50.3%	Headache, migraine
General disorders and administration conditions SOC	General system disorders NEC	73	40.3%	Chest pain, fatigue, oedema
Gastrointestinal disorders SOC	Gastrointestinal inflammatory conditions	71	39.2%	CD, enteritis, colitis
Gastrointestinal disorders SOC	Gastrointestinal motility and defaecation conditions	63	34.8%	Diarrhoea, constipation, GORD
Musculoskeletal and connective tissue disorders SOC	Joint disorders	59	32.6%	Arthralgia, arthritis, joint swelling, joint stiffness
General disorders and administration conditions SOC	Fatal outcomes	48	26.5%	Death, sudden cardiac death
Nervous system disorders SOC	Neurological disorders NEC	46	25.4%	Dizziness, paraesthesia
Skin and subcutaneous tissue disorders SOC	Epidermal and dermal conditions	46	25.4%	Rash, pruritus, dermatitis

Conclusions

As expected, the CDAI was the dominant composite index reported but there was significant variation in the selection and definition of clinical trial end-points in RCTs for CD between studies, and over time. Despite growth in reporting of objective measures of inflammation and in PROMs, there is much heterogeneity and lack of standardisation. This highlights the need for international researchers and clinicians to develop a COS for comparative effectiveness research in CD.

Summarising adverse events is complex due to difficulties in assigning cause to the treatment side effects, treatment failure or the underlying disease process. However, it is important and a COS should include key disease specific adverse events to indicate lack of efficacy and disease worsening. Consideration should also be given to treatment specific adverse events that might be added on to a COS.

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