Protocol

Title

The Quality of reporting Inflammatory Bowel Disease Randomized Control Trials: A systematic review

Authors

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Contributions of authors

JK and MG will independently review all title and abstracts through the conduction of a literature search, data extraction, and drafting of the final paper. Any disagreements were resolved by a third author.

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None.

Declaration of interests

None.

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None currently.

Background

Randomised controlled trials (RCTs) are the study of choice to provide reference standard evidence for the efficacy of new or existing interventions for the management of Inflammatory Bowel Disease (IBD) (1,2). Their methodological approach to reduce the risk of bias (any departure from the truth) ensures that the true effects of the intervention are reported in a manner that can best represent clinical reality.

In considering published RCTs, it is difficult to distinguish poor writing from poor research quality. Whilst studies all should report using the CONSORT guidance, released initially in 1995, many journals do not mandate this and often those that do simply confirm in a binary fashion (whether it is reported) rather than the appropriateness of what is recorded. As such, failing in such studies often leave readers having to assume poor reporting represents genuine bias. Whilst peer review can and should address this, there are long-standing concerns with the validity and reliability of this process with the field of academia, although it remains the best system and most used across publishing in the field.

Quality is a glib concept, capriciously employed and often a subjectively understood term. It has been further complicated in the last decade with the hugely significant emergence of a consensus on rating quality of a whole evidence base for each outcome through the use of GRADE (3). When considering individual RCTs, definitions of quality have often also varied, but most describe 'design and RCT conduct, to prevent systematic errors, or bias' (4). Bias occurs when the results of a study do not represent the truth because of the inherent limitations in the design or conduct of a study (5). As such, considering the risk of such bias is key when judging an individual RCT and failures in key areas can significantly limit the potential impact of a study.

The Cochrane risk of bias tool is employed across healthcare reviews to judge key elements which will be briefly summarised (6). Selection bias, which includes appropriate randomisation as its most obvious element, also includes the difficult to understand principle of allocation concealment. This was infamously demonstrated at the birth of the evidence base revolution over 25 years ago to lead to overestimates of treatment effect of close to 40% (7). This is best understood with an example. In an RCT investigating the use of biologic vs traditional oral therapies for IBD, an appropriate randomisation schedule may exist, and patients to be recruited from an outpatient setting. If the allocation schedule is available at recruitment, it is possible that a researcher who knows the next patient will be allocated a biologic therapy may choose not to recruit a subject who has difficult venous access. This sort of simple difference may lead to a systematic imbalance in the groups, with those patients with difficult venous access having a more complex historical course and being overrepresented in the control group. This example is key as it is not the same as blinding, which often is not possible for very practical reasons, but the concealment of the allocation schedule is always possible and a key source of potential bias.

Performance bias, through blinding of participants and personnel and detection bias, through blinding of outcome assessment, are better understood. Attrition bias occurs from missing outcome data and the more that is missing or unexplained, the more there is a risk that issues with adverse effects, tolerability or other negative outcomes could be misrepresented when ignored. Reporting bias is equally problematic with reporting of only advantageous outcomes, reporting of post hoc analysis or indeed the lack of reporting of key outcomes further raising the risk of bias.

A previous study of over 20,000 RCTs included in Cochrane reviews up to 2014 found that there was a trend towards improvement in all these key items of reporting (8). Within Inflammatory Bowel Disease, there is a relatively small evidence base on which treatments options emanate from and this is used to guide the treatment of hundreds of thousands of patients. In the last 5 years, almost all IBD international guideline committees have embraced the GRADE approach for quality assessment and recommendations. The key to the GRADE approach to risk of bias is that it is considered at the outcome and not individual study level. This means that the presence of individual studies that are reported in a manner that renders them of low risk of bias cannot prevent the overall certainty of the evidence for a given outcome being downgraded by studies at higher risk of bias (3). The implications of this, now and moving forward, are not yet fully understood by the entire IBD research and peer-reviewing community, but suggests that it is

more important now than ever before for all those producing and publishing RCTs to take all measures to report in a manner that is of low risk of bias, particularly as this allows true issues of quality to be separated from issues of reporting. This also ensures GRADE certainty of evidence can be the highest possible and not artificially impacted by such reporting issues.

Objectives

We set out to examine how reporting of these key elements of risk of bias within IBD RCT and factors associated with higher risk of bias through a systematic review of all IBD RCTs published since the Consort statement (1995).

Methods

To begin with, the systematic reviews will be searched for in the Cochrane library.

Inclusion criteria for systematic reviews:

Types of studies: Randomised controlled trails published since 1996 included in Cochrane reviews published by the Cochrane IBD group from March 2011 (launch of higgins criteria for risk of bias assessment - the last update of the Cochrane risk of bias reporting tool).

Type of participants: Patients with either Crohn's disease or Ulcerative colitis or a combination of the conditions to be included with all age groups and patients in any disease state to be considered.

Types of interventions: Interventions for the induction, maintenance, or management of symptoms. Studies could involve any form of intervention compared to any other intervention, placebo, no treatment or usual care. Studies could include any outcome measures.

Exclusion criteria for systematic reviews:

Systematic reviews published before March 2011 or duplicates from an earlier version of an already included review. Reviews that did not utilise the Cochrane risk of bias tool were not included.

Inclusion criteria for RCTs:

We will include all primary RCTs included in all included SR reviews from 1995 till the date of the search (July 2019), corresponding with the release of the CONSORT statement for trial reporting.

Exclusion criteria for RCTs: Quasi-randomised trials will be excluded

Search methods for identification of studies

We will use the latest update version of all titles included and will not include withdrawn titles or 'empty' reviews. Cochrane review will be downloaded as a PDF file from the Cochrane Library. All the included studies' publication characteristics and risk of bias assessment will be manually collected and recorded within a database file. Moreover, the PubMed and Web of Science databases will be downloaded with their list of indexed journals in addition to Journal Citation Reports.

Data collection and analysis

Data collection:

Two authors (JK and MG) will independently review all titles and abstracts of potential trials and then potential studies will be accessed in full text. Any disagreements will be resolved by a third author. All journal articles chosen for full-text review will be evaluated independently again by two authors (JK and MG) to assess inclusion criteria to consider for analysis, with the third author resolving differences. Extraction of the references for all included RCTs will occur first, followed by manual validation to exclude duplicates and references which were encompassed in multiple reviews.

Data extraction:

From included full-text RCTs, data will be extracted independently by 2 authors (JK and MG) using a standardized form to record the risk of bias for each item within the Cochrane Higgins criteria, as discussed above. Additionally, key demographic and descriptive data will be extracted, included the year of publication, journal source, number of authors, funding source and number of study centres.

A matching algorithm and manual validation will be used to standardise journal names and eliminate abbreviations. We will visit the website of each listed journal, if available, and extracted its up to date impact factor. The impact factor centile will then be collected from Journal Citation Reports.

The aforementioned publication characteristics will then be combined with the collected risk of bias assessment for each RCT, and as such, will be categorised as "low", "high", or "unclear" for each key risk of bias items as per sequence generation, allocation concealment, blinding, incomplete outcome data reporting, and selective reporting. The most recent risk of bias assessment will be considered for RCTs that were encompassed in multiple Cochrane reviews.

Analysis

The data will be first analysed to assess the proportion of trials at high and unclear risk of bias. This will then used to determine the evolution of poor reporting over time, its association to impact factor (No IF, <5, 5-10, ≥10), centile of impact factor (No IF, <70th centile, 70-90th, ≥90th

centile), funding source (industry and public sponsorship, public sponsorship, not specified, and industry), reported form (abstract, full text), study centre (single vs multi-centre), and number of authors (<5, 5-10, ≥10).

Ethics

Patients will not be involved at any stage of this study's design or outcome as data will be collected from previously published studies and at no point will patients be recruited.

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