Article

The Reporting of Sample Size Estimation in Randomised Trials of Inflammatory Bowel Disease: A systematic review

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The Reporting of Sample Size Estimation in Randomised Trials of Inflammatory Bowel Disease: A systematic review.

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Conclusions: Around half of the RCTs in IBD either do not report SSE or reach their recruitment target with the level of detail in reporting being limited.

Introduction.

The number of study participants or a sample size is an important factor to consider when designing a clinical trial. The larger the sample size, the more precise the results are and the higher the likelihood of detecting statistically significant results [1]. Studies with very small sample sizes may not be sufficiently powered to detect an important difference [2]. On the other hand, sample sizes that are too large can detect statistically significant differences even when they might not be clinically important [3]. This could result in the recommendation of treatments that are not effective. It is therefore important to carry out a sample size calculation.

Typically, a sample size estimation (SSE) would require the following components: the probability of a type I error (concluding that there is an effect when in reality there is not), probability of a type II error (concluding that there is no effect when in reality there is), minimal clinically important difference (the smallest difference in means that you regard as being important to be able to detect) and standard error [3]. These tests are so sensitive that small differences in any of the components could lead to a wide variation in the estimates [4].

The reporting of sample size estimation in randomised controlled trials (RCTs) has become a standard requirement since the Consolidated Standards of Reporting Trials (CONSORT) statement was published in 1996 [5]. The improvement of power calculation reporting since the publication of the CONSORT statement has been seen [6].

Achieving an optimal sample size can improve the precision of trial results. For systematic reviews, a meta-analysis of data from multiple studies has offered the promise of addressing the weaknesses in an evidence base made up of underpowered studies. Proponents of evidence-based medicine maintain that by pooling data from multiple studies, regardless of a

sample size of individual studies, power and the likelihood of achieving precision is enhanced in systematic reviews [7]. However, the issue of imprecision persists in systematic reviews as a recent study found that 65% of Cochrane systematic reviews had imprecise results[8]. Given that current methods (the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach) of assessing the precision of systematic evidence from optimal information sizes tend to rely on adequate reporting of sample size estimation [9,10] poor practice in sample size estimation can impact the certainty of outcomes.

Additionally, studies with sub-optimal small sample sizes may seem unethical for a number of reasons. Primarily, the risks participants undergo are not compensated by the potential of the trial to detect meaningful or clinically important estimates [11]. Additionally, the financial costs and practical implications of the time commitment needed by researchers or patients must be based on the assumption that a study is able to address its hypothesis and in the case of an underpowered study, this will never be the case.

Research investigators fail to recruit the number of participants stipulated in their sample size calculation for various reasons. For Inflammatory Bowel Disease (IBD) trials, this may be due to certain elements of study design such as randomisation and blinding, frequency of visits, invasiveness of intervention or need for colonoscopy/sigmoidoscopy [12]. Most studies on key IBD outcomes usually involve some or all these factors, but as they are essentially predictable, designing studies to mitigate such issues should always be possible. This study set out to systematically review the whole body of published IBD RCTs to identify the reporting of power calculations and the nature of these calculations.

Methods.

This review was performed in alignment with Cochrane guidelines [13] in June 2019 and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. A protocol for the review is available for the analysis [15].

Search methods for identification of studies.

Electronic searches.

We conducted a comprehensive search of the Cochrane IBD Specialized Trials Register, CENTRAL and hand searched within the Cochrane library of IBD reviews for further primary RCTs. We included RCTs published since 1996 (after the publication of the CONSORT statement). We excluded cluster RCTs; pilot or feasibility studies; studies with mixed population of people with and without IBD; studies on secondary analyses of follow-up data collection after discontinuation of treatment. We included abstracts if information was available to judge inclusion. If not available, we contacted authors, and if there was no response, we excluded.

Types of participants.

People of any age with inflammatory bowel disease.

Types of interventions.

Any therapeutic intervention when compared with any other intervention, placebo or no treatment.

Using the above search strategy, two review authors (SL and DA) identified RCTs titles that appeared to be potentially relevant. These were independently screened and in circumstances of disagreement, a third review author (ZIE) was involved to reach consensus.

Data extraction and management.

We developed a data extraction form and used it to extract information on relevant features and results of included studies. Two review authors (SL and DA) independently extracted and recorded data on a predefined checklist. When disagreements occurred, a third review author (ZIE) was involved and consensus was reached. The fourth author (VS) then reviewed the completed data extraction form and checked it with the studies used.

The main outcome was to assess the proportion of studies reporting power calculation, the reproducibility of such calculations. The secondary outcomes were to compare the differences studies used and the sample sizes involved.

Extracted data included the following items.

Characteristics of participants: disease type and state;

Presence of sample size estimation and calculation details (MCID, power, significance level, target sample size);

Total number of participants originally assigned to each group;

Intervention and control details;

Outcomes: the achievement of target sample size; number of patients recruited and completing study; number of treatment success / failures; the MCID proposed and the difference achieved; whether the studies are underpowered and by how many people; adverse events; and definitions of the outcomes;

We resolved inconsistencies in data extraction and transferred the information above into the Characteristics of the included studies table.

Data synthesis.

We produced descriptive statistics regarding the overall rates of sample size calculation and pooled studies with the same population, intervention, comparator, and outcomes.

Ethical statement.

As all data included already existed within published scholarly output, no ethical approval was sought.

Results.

The search performed in June 2019 revealed 765 RCTs (697 after duplicates removal). Initial titles screening excluded 418 studies leaving 279 articles for further assessment. The reasons for exclusion: published before 1996 (117 studies), the wrong patient group or wrong diagnosis (301 studies). 279 articles were further assessed, and 47 of them were excluded with reasons: published as abstracts with insufficient information (30 studies), pilot/feasibility studies (11 studies), non-RCTs (2 studies), or not written in the English language (4 studies). This left 242 studies (reported in 232 publications) to be included (see Figure 1).

Of the 242 included studies, 116 studies were on Ulcerative Colitis (UC) (48%) (84 induction and 32 maintenance), 99 on Crohn's Disease (CD) (41%) (54 induction and 45 maintenance) while 27 studies were on other conditions within IBD (11%). There were more studies on UC than CD. The reference list of the included studies can be found in the Appendix 1. Full extracted data is available from the team on request. We carried out a subgroup analysis by disease type, disease state and drug class (Table 3), and performed chi-square analysis between the drugs classes as well as between induction and maintenance studies (o.o5 significance level). There was no difference in reporting of SSE between immunomodulators and microbiome subgroups (p=0.067797; 101 SSE/30 no SSE immunomodulators, 49/26 microbiome); maintenance and induction studies (p=0.360891; 70/27 maintenance, 119/35 induction) as well as between biologics and immunomodulators (p=0.50793, 52/12 biologics, 101/30 immunomodulators). The difference between biologics and microbiome (p=0.035853; 52/12 biologics, 49/26 microbiome) is statistically significant. The difference between CD and UC studies is statistically significant (p=0.003627; 90/130 CD, 99/32 UC).

About 25% (59/242) of the studies failed to report on sample size estimation. In CD studies, reporting was more common in inactive (80%) compared to active (72%) disease studies. Of the 183 studies which reported sample size estimation, 61 (33%) failed to recruit their target sample size. Studies on UC (67%) were more likely to meet their target sample size than CD studies (61%) though not by substantial difference (Table 1; Figure 2). For the studies which failed to meet their recruitment target, the mean sample size deficit was about 31% and ranged from 21 to 40%.

The sample size calculation reported in the studies were assessed for reproducibility. Most of the studies failed to report sufficient information for their sample size to be replicated. There were 99 two-arm superiority trials of which only 35 studies (35%) reported sufficient information to enable the replication of sample size estimation. However, we managed to replicate sample sizes of 71 studies (71%) in total using parameters proposed in the protocol. The reported sample size was equal to the recalculated estimate in 8 studies (11%), higher in 43 studies (61%), and lower in 19 studies (27%). The difference between the reported and recalculated was up to 10% in 20 (28%) studies, 20% in 19 (27%) studies, and over 20% in 24 (34%) studies.

There was variation across studies in the parameters used in their sample size estimation (Table 2). However, the majority of the studies used 80% power, probability of type I error was 0.05 and the most commonly reported minimal clinically important difference ranged from 20 to 30%.

Discussion.

The aim of the study is to examine the reporting of sample size estimations in IBD trials. To achieve this, we found 242 RCTs (reported in 233 publications) assessing the effectiveness of interventions used in managing IBD. The results showed that sample size estimation was reported in 75% of the studies. This finding is also consistent with previous reports [6]. However, a third of those that did report sample size estimation, failed to meet the recruitment target specified in their study, meaning that half of all included trials did not report sample size estimation or meet their required target. When we examined reporting trends in by disease type and purpose of the intervention, the purpose of the intervention (induction or maintenance) appeared to impact on successful recruitment in UC studies, however, this is not the case in CD studies. This adds to the knowledge on barriers to study recruitment in IBD [12]. In the studies which failed to meet their recruitment target, reported sample size deficits ranged from 29 to 40%, significantly underpowering the subsequent output. Our chi-square analysis showed that maintenance studies are better at reporting sample sizes than induction studies. The reason for this is unclear, and further research into this topic is required. Studies on biologics are better at reporting SSE than studies on immunomodulators. This can be because studies on biologics are generally newer, hence, they are more likely to report on SSE.

To assess whether the sample size estimates were reliable, we attempted to recalculate the study sample sizes and found that the studies rarely (35%) provided full details to enable replication. Although we were able to recalculate study sample sizes for a substantial proportion (71%) of the eligible studies, this was only enabled by our use of agreed default values for the sample size parameters and hypothesis testing. This finding is also consistent

with similar reviews on anaesthesia and osteoarthritis trials which found only a small proportion of studies reporting sufficient details to enable replication of their sample size estimations [16, 17]. When we recalculated the sample sizes for this review, around 90% of the studies assessed were found to have overestimated or underestimated the required sample size. Overestimation of sample size was expectedly more common as that trial investigators tend to inflate sample sizes to account for drop-out and withdrawal due to adverse events. This finding should be interpreted with caution as due to partial reporting of sample size estimation details in the studies, some of the recalculated estimates may not accurately reflect the estimations carried out by the trial investigators.

These findings support the shift by evidence producers like Cochrane from emphasising on statistical significance to clinical importance. It also shows that having multiple studies with small sample sizes do not eliminate the need for single well-powered RCTs. In most studies, it was unclear what whether the parameters for their SSE's were informed by the broader literature or clinical experience. Future research should assess parameters of sample size estimation which determine whether meaningful results will be obtained for specific outcomes. This will determine whether there is any consensus on what is considered a 'meaningful' result for specific outcomes in IBD trials and form a useful resource for future researchers. Also, considering if poor reporting of SSE is correlated with other areas of reporting, comparing with the Cochrane risk of bias tool, for example, would be useful. This would allow the subgroup analysis for other factors, such as different disease types or settings.

We were aware of potential biases in the process of conducting this review and put in measures to minimise them, however, there are decisions that were made during the process

which may have introduced limitations. As a result, due to a large number of studies found, we attempted to minimise errors by involving two authors at the data extraction phase while additional checks were carried out by a third author. We encountered difficulties dealing with a lack of clarity and incompleteness in the reporting in the studies in ways that were not anticipated at the protocol phase. For instance, we had concerns about two studies which appeared to have estimated sample sizes retrospectively, a study indicated that sample size estimation was not done statistically, and two studies described as being 'exploratory' in nature which may have been wrongly included. The decision to include or exclude these studies from the analysis could be regarded as study limitations, however, given the small numbers we do not expect these studies to have a substantial impact on the results. We did not contact authors for clarification due to the number of studies we found, only authors of abstracts, and we excluded four studies that were not in English.

Conclusions.

In summary, around half of the RCTs in IBD either do not report SSE or reach their recruitment target. When studies do report on sample size estimation, the level of detail in reporting is limited. The results of this study provide an insight into the current practices of reporting SSE highlighting the need for discussions on how to utilise them to better use in primary trials and systematic reviews.

Whilst reaching the recruitment target is expected to produce meaningful results in the studies, a third of the studies are not recruiting successfully. Even when studies can successfully reach their target sample size, it is uncertain whether it is sufficient to detect a meaningful result.

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Authorship.

Guarantor of the article: Morris Gordon.

Author contributions: ZIE initiated and conceptualised the review, SL, DA, VS collected data, ZIE, MG contributed to design of the study and drafted the manuscript, which was adjusted to the journal format by SL. AA supported the review, contributed to the manuscript. All authors approved the final manuscript.

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Table 1: Reporting of sample size estimation based on disease type and purpose of intervention.

Abbreviations: CD, Crohn's Disease; UC, Ulcerative Colitis.

Table 2: Details of sample size estimation and parameters reported in studies.

Table 3: Subgroup analysis of the included studies.

Abbreviations: SSE, sample size estimation; CD, Crohn's Disease, UC, Ulcerative Colitis.

Figure 1: Flow diagram of the study selection process.

Abbreviations: UC, ulcerative colitis; CD, Crohn's Disease; RCTS, Randomised Controlled Trials.

Figure 2. Sample size estimation and recruitment success.

Abbreviations: SSE, sample size estimation; SSD, sample size deficit; UC, ulcerative colitis; CD, Crohn's Disease.

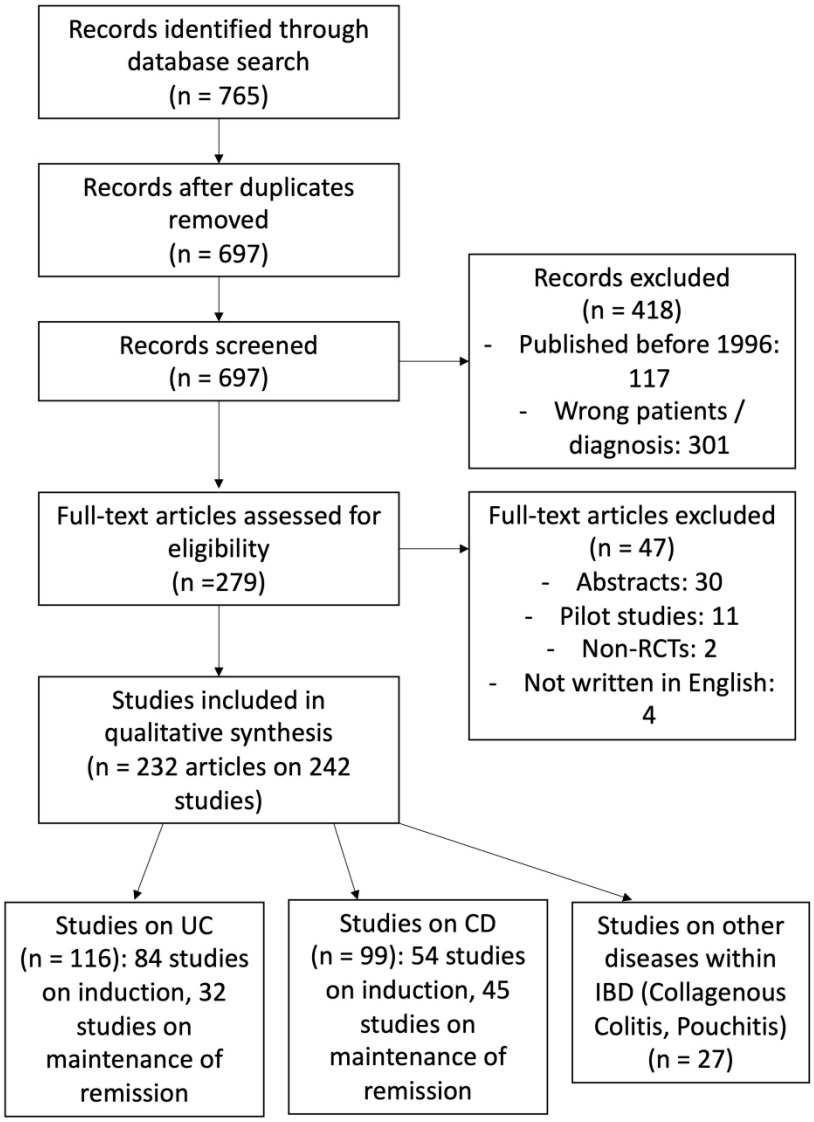

Figure 1: Flow diagram of the study selection process.
Abbreviations: UC, ulcerative colitis; CD, Crohn's Disease; RCTS, Randomised Controlled Trials.

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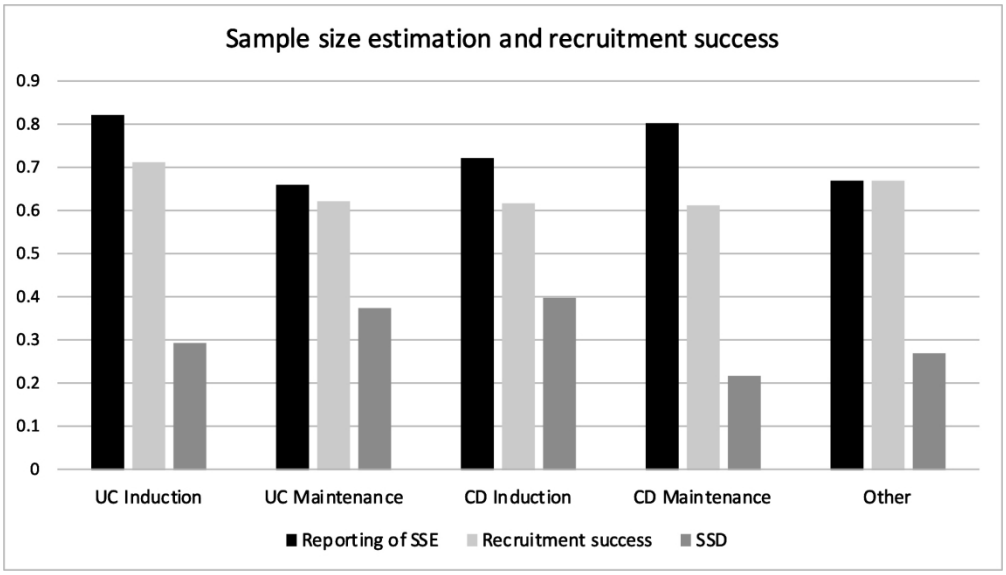

Figure 2. Sample size estimation and recruitment success.
Abbreviations: SSE, sample size estimation; SSD, sample size deficit; UC, ulcerative colitis; CD, Crohn's Disease.

171x97mm (300 x 300 DPI)

Table 1.

Reporting of sample size estimation based on disease type and purpose of intervention.

Disease type/purpose	Total	Estimation reported	Estimation not reported	% reporting	Recruitment success	Recruitment failure	%recruitment success	% sample size deficit
UC/induction	84	69	15	82.1%	48	17	69.6%	29.2%
UC/maintenance	32	21	11	65.6%	13	7	61.9%	37.4%
CD/induction	54	39	15	72.2%	24	15	61.5%	39.6%
CD/maintenance	45	36	9	80.0%	22	13	61.1%	21.4%
Other	27	18	9	66.7%	12	9	66.7%	27.0%
Total	242	183	59	75.6%	119	61	49.2%	31.0%

Abbreviations: CD, Crohn's Disease; UC, Ulcerative Colitis.

Table 2.

Details of sample size estimation and parameters reported in studies.

Sample size estimation reported:	183 (75.6%)
Not reported:	59 (24.4%)
Target sample size achieved:	119 (65%)
Not achieved:	61 (33.3%)
Sample size deficit (n = 61)	
Up to 10%:	15 (24.6%)
>10 to 20%:	10 (16.4%)
>20%:	34 (55.7%)
Sample size recalculation (n = 183)	
Parameters fully reported:	35 (19.1%)
Partially reported:	65 (35.5%)
Non-inferiority trials:	17 (9.3%)
Three arm trials:	57 (31.1%)
Studies with continuous outcome:	9 (4.9%)
Power of study (n = 67)	
0.54:	1 (1.5%)
0.2:	44 (65.7%)
0.19:	1 (1.5%)

0.17:	1 (1.5%)
0.15:	2 (3%)
0.14:	1 (1.5%)
0.11:	1 (1.5%)
0.10:	16 (23.9%)
Type I error (alpha) (n = 63)	
0.05:	58 (92%)
0.025:	3 (4.8%)
0.017:	1 (1.6%)
0.001:	1 (1.6%)
Minimal clinically important difference (n = 101)	
Up to 10%:	5 (5%)
>10 to 20%:	31 (30.7%)
>20 to 30%:	35 (34.7%)
>30%:	30 (29.7%)
Reported versus calculated sample size estimation (n = 71)	
Identical:	8 (11.3%)
Less than calculated:	19 (26.8%)
More than calculated:	43 (60.6%)

Difference between reported and calculated estimation (n = 62)	
Up to 10% difference:	20 (32.3%)
>10 to 20% difference:	19 (30.6%)
>20% difference:	24 (38.7%)

Table 3. Subgroup analysis of the included studies.

Drug Categories	CD Induction		CD Maintenance		UC induction		UC maintenance		Other		Total	
	Total papers (%)	SSE reported (%)	Total papers (%)	SSE reported (%)	Total papers (%)	SSE reported (%)	Total papers (%)	SSE reported (%)	Total papers (%)	SSE reported (%)	Total papers (%)	SSE reported (%)
Biologics	17 (7%)	16 (94%)	8 (3%)	5 (63%)	34 (15%)	28 (82%)	4 (2%)	2 (50%)	1 (1%)	1 (100%)	64 (27%)	52 (81%)
Immunomodulators	21 (9%)	16 (76%)	35 (15%)	30 (86%)	38 (16%)	28 (74%)	27 (12%)	21 (78%)	10 (4%)	6 (60%)	131 (56%)	101 (77%)
Microbiome	27 (12%)	16 (59%)	12 (5%)	7 (58%)	17 (7%)	15 (88%)	11 (5%)	5 (45%)	8 (3%)	6 (75%)	75 (32%)	49 (65%)

Abbreviations: SSE, sample size estimation; CD, Crohn's Disease, UC, Ulcerative Colitis.

Appendix 1.

Included studies:

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