Διπλωματική εργασία

Assessing the reporting quality of RCTs for Infliximab in Crohn's disease published from 2000 to 2019 using the CONSORT statement

Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων κλινικών δοκιμών για τη χρήση του infliximab στη νόσο Crohn, που δημοσιεύτηκαν από το 2000 έως το 2019, με τη χρήση των

Πανεπιστήμιο Θεσσαλίας

Τμήμα Ιατρικής

Πρόγραμμα μεταπτυχιακών σπουδών

' Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Βιοπληροφορική '

Τριμελής Συμβουλευτική Επιτροπή: κ. Στεφανίδης Ιωάννης

κ. Δοξάνη Χρυσούλα

κ. Ζιντζαράς Ηλίας

Φοιτήτρια: Παπατζέλου Ιωάννα

Έτος: 2019

Abstract

Introduction: The complete and adequate reporting of RCTs is of extreme importance as it aids the concrete and free of bias clinical decision making.

Objectives: The aim of this study was to assess the reporting quality of RCTs for infliximab in Crohn's disease based on the (CONSORT) statement.

Methods: Pubmed was searched for relevant articles. The reporting frequencies of the 37 subitems of the CONSORT checklist were analyzed overall, according to the IF of the journal and the year of publication (pre-or post- 2010).

Results: 20 RCTs were included in the study. The overall compliance with the CONSORT statement was adequate, as 73% of the subitems were reported in >75% of the included trials. 32% of the subitems were reported in all the studies. There was an implication for a better compliance of the higher ranked journals, compared with the lower ranked, which was not found to be statistically significant. No better reporting was found in 10 out of the 11 subitems that were added in the 2010 version, between studies published before and after 2010.

Conclusion: Although the study showed an overall good compliance of the included articles with the CONSORT statement, there were still deficiencies regarding key aspects of RCTs, which emphasizes the need for further improvement.

Keywords: infliximab, Crohn's disease, randomized control trials, CONSORT statement, reporting quality

Εισαγωγή: Η πλήρης και επαρκής αναφορά των κλινικών μελετών έχει ιδιαίτερη σημασία καθώς συμβάλλει στην λήψη ορθών κλινικών αποφάσεων.

Στόχοι: Βασικός σκοπός αυτής της έρευνας ήταν η αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων κλινικών δοκιμών για τη χρήση του infliximab στη νόσο Crohn με βάση τα κριτηρια CONSORT.

Μέθοδοι: Η μηχανή αναζήτησης pubmed χρησιμοποιήθηκε για την ανεύρεση σχετικών δοκιμών που δημοσιεύτηκαν από το 2000 έως το 2019. Η συχνότητα αναφοράς των 37 κριτηρίων του καταλόγου CONSORT στις μελέτες αυτές αναλύθηκε συνολικά, με βάση τη βαθμολογία του περιοδικού στο οποίο δημοσιεύτηκε η κάθε έρευνα και του έτους δημοσίευσης (πριν και μετά το 2010).

Αποτελέσματα: 20 κλινικές δοκιμές συμπεριλήφθηκαν στην έρευνα. Η συνολική συμμόρφωση στα κριτήρια του καταλόγου κρίθηκε ικανοποιητική, καθώς το 73% των κριτηρίων καταγράφηκαν επαρκώς σε ποσοστό>75% των ερευνών. 32% των κριτηρίων καταγράφηκαν από όλες τις έρευνες. Τα περιοδικά με μεγαλύτερο IF φάνηκε να παρουσιάζουν καλύτερη συμμόρφωση στα κριτήρια συγκριτικά με τα μικρότερης βαθμολογίας περιοδικά, διαφορά που όμως δεν κρίθηκε στατιστικά σημαντική. Στη σύγκριση με βάση το έτος δημοσίευσης δεν ανευρέθηκαν επίσης σημαντικές διαφορές.

Συμπεράσματα: Παρά την ικανοποιητική συμμόρφωση, η ποιότητα αναφοράς των κλινικών δοκιμών επιδέχεται περαιτέρω βελτίωσης, καθώς παρατηρήθηκε ελλιπής καταγραφή κριτήριων που αναφέρονται σε σημαντικά σημεία της διεξαγωγής των κλινικών δοκιμών.

Λέξεις κλειδιά: infliximab, Crohn’s disease, CONSORT STATEMENT, ποιότητα αναφοράς

Introduction

Crohn's disease is an idiopathic, chronic, inflammatory disorder of the gastrointestinal tract with an increasing incidence and prevalence over the past decades. Together with ulcerative colitis, they make up the medical condition known as inflammatory bowel disease (IBD). Crohn's disease mainly affects young adults aged 15-35 years old, although there is an increasing number of children that are being diagnosed each year. According to the literature the incidence ranges from 3,1 to 14,6 cases per 100.000 person years and the prevalence is 201 per 100.000 adults. The disease seems to be following a north to south pattern and is more common in urban areas.[1]

The disease is characterized by transmural inflammation and segmental involvement of the gastrointestinal tract and it can affect any component of it (from anus to the mouth). The small bowel and especially the distal ileum are the most commonly affected parts. The typical clinical manifestations involve crampy abdominal pain, chronic diarrhea and fatigue. Systematic symptoms such as fever and weight loss are also common. The disease is associated with several extraintestinal manifestations (arthritis, eye and skin disorders, primary sclerosing cholangitis, amyloidosis, renal stones, osteoporosis, thromboembolism) and can lead to serious complications such as bowel stenosis and the formation of abscesses and fistulas. The diagnosis is based on the clinical features and confirmed by the following endoscopic, imaging and histologic findings.[2]

The pathogenesis of Crohn's disease remains uncertain. Genetic, microbial and immune factors seem to contribute to it. More specifically, both endogenous genetic and external factors can lead to an imbalanced immune response to the microbes of the intestinal lumen. This dysregulated response comprises all parts of the immune system (innate and acquired) and is characterized by dysregulation in the epithelial barrier, in the activation of immune cells and the secretion of inflammatory/regulatory mediators (cytokines). Tumor necrosis factor alpha (TNFa), one of the most studied proinflammatory cytokines, has been found to be overly secreted in patients with Crohn's disease. These findings are consistent with observations from mouse models with colitis, emphasizing the critical role of the TNFa in the enhancement of intestinal inflammation in Crohn's disease.[3]

Treatment options include:

- Induction of remission: 5-ASA (sulfasalazine/mesalamine), corticosteroids, immunomodulators (methotrexate, azathioprine) and biologic factors (anti-TNF-agents infliximab, adalimumab, certolizumab pegol; agents targeting leukocyte trafficking, including vedolizumab, natalizumab; and the anti-p40 (anti-IL-12/23) antibody, ustekinumab)
- Maintenance of remission: azathioprine/methotrexate ± anti-TNF agents
- Fistulizing Crohn's disease: Infliximab, adalimumab, certolizumab, thiopurines (azathioprine, 6-mercaptopurine), tacrolimus, imidazole antibiotics, drainage, placement of setons
- Postoperative Crohn's disease: imidazole antibiotics, thiopurines, anti-TNF agents
- Treatment of complications: Surgery[2,3]

Corticosteroids have been the traditional first line therapy for patients with active Crohn's disease. However, a significant percentage of patients 1/3 become steroid dependent and another 1/3 are steroid resistant. Furthermore, a prolonged administration of corticosteroids is associated with concerning adverse effects. Immunomodulators have been the alternative steroid sparing treatment option for patients with Crohn's disease, prior to the introduction of biologic agents in the late 1990s. Immunomodulators have a slow time to clinical response, are not effective in inducing clinical remission (with the exception of methotrexate) and are also associated with toxicity and adverse events.

Biologic factors target specific stages of the inflammatory cascade of the disease and have been found to be effective for the induction and maintenance of Crohn's disease. Infliximab (IFX) is a chimeric mouse/human monoclonal IgG1 antibody comprised of 75% human and 25% murine sequences, which has a high specificity for and affinity to TNF-α. It thus works by neutralizing the biologic activity of TNF-α after inhibiting binding to its receptors.[4]

Summing up, Crohn's disease is in most cases a chronic, progressive and destructive condition, which severely impacts the quality of life of the patients. It is, thus, of outmost importance that available data concerning the treatment options are clearly and adequately reported.

Randomized control trials remain the gold standard for the evaluation of a new treatment/ intervention. They are experiments, in which one (or more) group of people receiving the tested intervention, is being compared with another group of people receiving a different intervention. Randomization, the random allocation of the trial subjects to the possible interventions is a way of reducing certain kind of bias.

CONSORT stands for Consolidated Standards of Reporting Trials and its main products are a statement consisting of a 25-item list and a flow diagram. The statement represents 'an evidence-based minimum set of recommendations for reporting randomized trials'.[5] It is a useful tool aiming to improve the reporting quality of RCTs, thus guaranteeing that appraisal of new interventions and clinical decisions are based upon complete and accurate evidence.

The CONSORT statement was first published in 1996 and revised twice, in 2001 and 2010. The last update of the statement in 2010 is the one used currently. There are some extra items added in the last revision, compared with the first one, and more specifically:

- Item 1b: structured summary of trial designs, methods, results and conclusions
- Item 3a: Description of trial design, including allocation ratio
- Item 3b: important changes to methods after trial commencements with reasons
- Item 6b: any changes to trial outcomes, after the trial commenced, with reasons
- Item 11b: description of the similarities of interventions
- Item 13b: for each group losses and exclusions after randomization together with reasons
- Item 14b: why the trial ended or was stopped

- Item 17b: for binary outcomes, presentations of both absolute and relative effect sizes
- Item 23: registration number and name of trial registry
- Item 24: where the full trial protocol can be assessed
- Item 25: sources of funding and other support

The aim of this study is to assess the reporting quality of RCTs for infliximab in Crohn's disease published from 2000 to 2019, using the CONSORT statement.

Methods

This is an observational study of RCTs concerning infliximab for the treatment of Crohn's disease, published from 2000 to 2019.

Search strategy and study selection

Pubmed database was searched in August 2019 with the search terms 'infliximab' AND 'Crohn's' and the additional filters of publication date (2000-2019) and article types (clinical trial).

The titles and abstracts of the retrieved articles were assessed to check if they met the eligibility criteria, which were a) pivotal randomized control trials, b) assessing the role of infliximab in Crohn's disease, c) written in English language and d) published from January 2000 to the date of search (August 2019). To be considered as an RCT, a trial should entail at least two arms of randomized trial subjects, receiving the compared interventions. Secondary analyses and meta-analyses of previous reported RCTs, economic evaluations, pilot studies or studies assessing the infliximab biosimilar CT-P13 were excluded from the study. However, the references of those publications were screened for studies matching the eligibility criteria, unidentified by the initial search. There were no limitations regarding the age, sex or origin of the participants. The initially selected studies were then evaluated in full text to confirm their eligibility.

Consort 2010 adherence

The reporting quality of the RCTs was assessed using the 2010 CONSORT checklist, (http://www.consort-statement.org/consort-2010), which consists of 37 (sub)items. The studies were read in full text and assessed based on the adequate report of the 37 subitems. All items were investigated in terms of whether they were reported and not whether they were carried out during the trial. Items adequately reported were scored with 1, those inadequately or not at all reported were scored with 0. Some of the subitems are not applicable in every single study (e.g. subitem 14b). When applicable in the study and adequately reported, the item was scored as 'adequately reported'. When possible, but not reported, the item was scored as 'inadequately reported. When not applicable and not reported the item was still scored as adequately reported. Any unclear answer was considered negative. Thus, there was a total final score for each included study, with the maximum possible score being 37.

Evaluation and Statistical analysis

The journals of the eligible articles were separated into two groups, depending on their ISI (Institute for Scientific information) Impact Factor 2018, as high and low ranked. The mean of the impact factors of the journals included in the trial was used as the cutoff point (20). This was done in order to examine whether there was a tendency for better RCTs reporting in higher ranked journals.

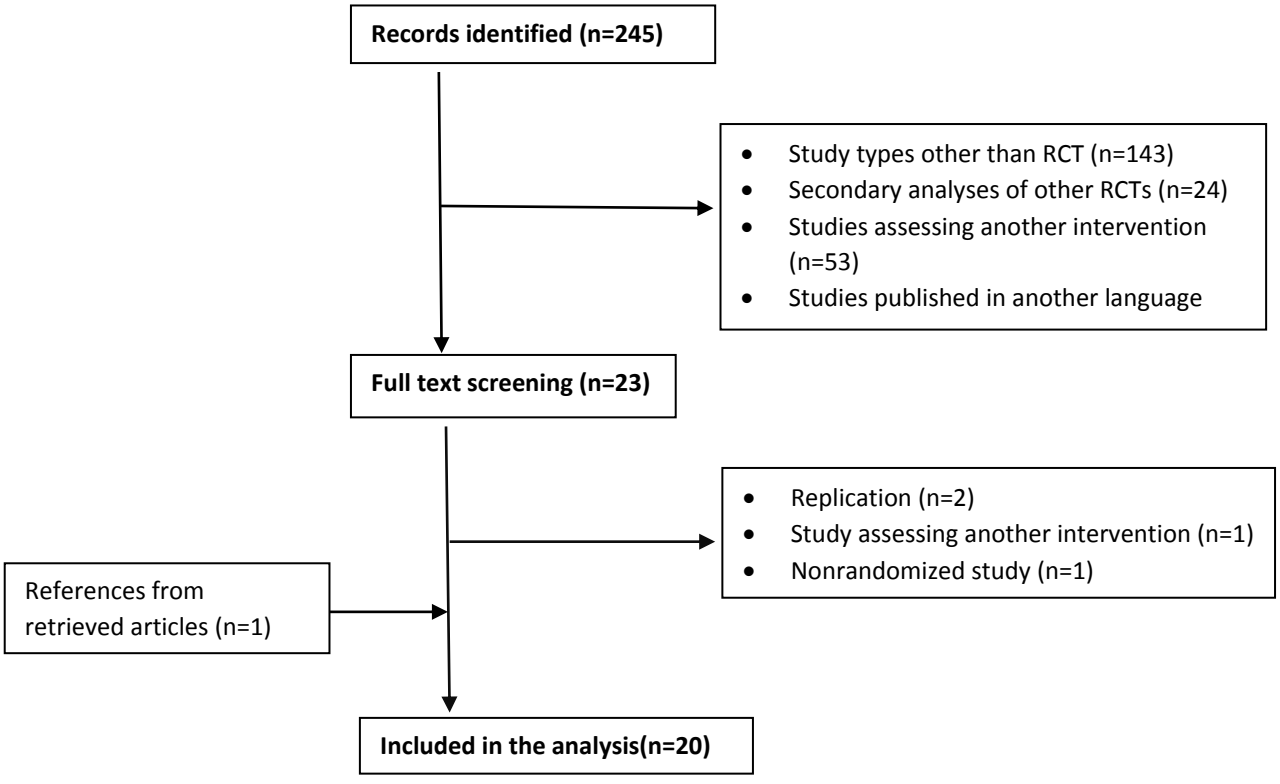
The articles were also grouped depending on the year of their publication (before and after 2010), as 2010 was the year of the last revision of the CONSORT statement. Since there were 11 items added after the last revision, the reporting quality of those items was assessed over the chronic point of their addition to the checklist.

The frequencies of the reported items were analyzed overall, according to the ranking of their journal of origin (IF) and the year of their publication. The comparisons were made with the use of the Fisher exact test. Given the small sample size of the study (n=20) the chi square test was considered inapplicable. Frequencies were calculated and statistical tests were performed using the IBM SPSS Statistics package version 25, provided by the University of Thessaly. A p value of 0.05 was set as the threshold for statistical significance.

Results

Eligible studies

The initial search identified 245 items. 222 of them were rejected by the first screening, because they did not fulfil the inclusion criteria. The remaining 23 records were followingly assessed in full text. Two of them were replications and another two did not meet the inclusion criteria. 1 study identified by the references of a relevant meta-analysis was added in the accepted records. Thus, a total of 20 studies were included in the analysis. (Figure 1).



Study characteristics

The eligible studies were published in 9 different journals (figure 2). In detail, 14 of the studies were retrieved from higher ranked journals (IF >20, cutoff mean value) and 6 of them from lower ranked (IF<20). The articles were published from 2001 to 2018, all of them after the introduction of the CONSORT statement. 11 of them were published prior to the 2010 revision and 9 of the after it. In most of the studies the subjects were adults, only two of them addressed children.

Journal	Number of RCTs	Impact factor
New England Journal of Medicine	2	70.670
The Lancet	2	59.101
Gastroenterology	9	20.877
The Lancet Gastroenterology and Hepatology	1	12.061
Journal of Crohn's and Colitis	1	7.82
Alimentary Pharmacology & Therapeutics	1	7.73
Inflammatory Bowel Diseases	2	4.065
Journal of Pediatric Gastroenterology and Nutrition	1	3.015
Surgery Today	1	2.077
Year of publication		
Prior to 2010	11	
After 2010	9	

Figure 2 Characteristics of the studies included in the analysis

Main Results

Table 1 shows the frequency of reporting of each one of the 37 subitems of the CONSORT checklist. The overall reporting of each subitem ranged from 5% to 100 %. 22 out of the 37 subitems (59%) were adequately reported in ≥ 90% of the included studies, 5 (14%) in 70-90% of them, 6 (16%) in 50-70% and 4 (11%) had a reporting score of less than 50%. The subitems reported in less than half of the studies were subitems no 9 and 10 (randomization methods), 17b (presentation of binary outcomes) and 24 (protocol). A total of 12 out of the 37 subitems (32%) was adequately reported in all of the studies, those being subitem 1b (structured summary), 2a,2b(introduction), 3b (changes to methods), 5(interventions), 6b (changes to trial outcomes), 7b(interim analyses), 11a(blinding), 12a (statistical methods), 14a (dates of recruitment and follow up), 17a (outcomes and estimations) and 22 (interpretation).

When comparing the reporting of each subitem according to the IF of the publishing journal, statistically significant differences were found in only 2(6%) out of the 37 reported subitems (table 1). Another 3 items (8%) presented a marginally significant difference. In all of them, it was the higher ranked journals that complied better to the CONSORT checklist. The relevant subitems were subitem no 7a(sample size determination), 12b(methods for additional analysis), 13a (participant flow), 18 (ancillary analysis) and 19 (harms).

Consort items	Overall % of reporting item (n=20)	% of reporting item		p value
		Journals with IF>20 (n=14)	Journals with IF>20 (n=6)	
1a	50 (10)	43 (6)	67 (4)	0.62
1b	100 (20)	100 (14)	100 (6)	1.00
2a	100 (20)	100 (14)	100 (6)	1.00
2b	100 (20)	100 (14)	100 (6)	1.00
3a	50 (10)	64 (9)	17 (1)	**0.14**
3b	100 (20)	100 (14)	100 (6)	1.00
4a	90 (18)	93 (13)	83 (5)	0.52
4b	90 (18)	86 (12)	100 (6)	1.00
5	100 (20)	100 (14)	100 (6)	1.00
6a	95 (19)	93 (13)	100 (6)	1.00
6b	100 (20)	100 (14)	100 (6)	1.00
7a	80 (16)	93 (13)	50 (3)	**0.06**
7b	100 (20)	100 (14)	100 (6)	1.00
8a	60 (12)	64 (9)	50 (3)	0.64
8b	85 (17)	93 (13)	67 (4)	0.20
9	10 (2)	7 (1)	17 (1)	0.52
10	25 (10)	21 (3)	33 (2)	0.61
11a	100 (20)	100 (14)	100 (6)	1.00
11b	65 (13)	64 (9)	67 (4)	1.00
12a	100 (20)	100 (14)	100 (6)	1.00
12b	85 (17)	100 (14)	50 (3)	**0.01**
13a	90 (18)	100 (14)	67 (4)	**0.07**
13b	80 (16)	76 (11)	83 (5)	1.00
14a	95 (19)	100 (14)	83 (5)	0.30
14b	100 (20)	100 (14)	100 (6)	1.00
15	95 (19)	100 (14)	83 (5)	0.30
16	95 (19)	100 (14)	83 (5)	0.30
17a	100 (20)	100 (14)	100 (6)	1.00
17b	35 (7)	43 (6)	17 (1)	0.35
18	90 (18)	100 (14)	67 (4)	**0.07**
19	85 (17)	100 (14)	50 (3)	**0.01**
20	90 (19)	93 (13)	83 (5)	0.52
21	50 (10)	64 (9)	17 (1)	0.14
22	100 (20)	100 (14)	100 (6)	1.00
23	60 (12)	57 (8)	67 (4)	1.00
24	5 (1)	7 (1)	0 (0)	1.00
25	90 (18)	93 (13)	83 (5)	0.52

Table 1 Reporting of CONSORT items, overall and according to IF

The majority of the studies had an adequate overall compliance to the CONSORT statement (figure 2). 1 out of the 20(5%) studies had an overall compliance >90%, 17(85%) of them had a compliance of 70-90% and only 2 (10%) studies had a compliance <70%.

Assessed according to the IF of the publishing source, the overall compliance (< or > than 70%) showed a difference in favor of the higher ranked journals, that was not proved to be statistically significant(p=0.07). In detail, all the articles deriving from high ranked journals had a compliance >70%, as compared with 67% of the articles from lower ranked journals

(table 2). The latter implicates a possible association between IF and a better CONSORT adherence.

compliance	<70%	70-90%	>90%
Total (n=20)	2 (10%)	17(85%)	1 (5%)
IF>20 (n=14)	0 (0%)	13(92%)	1 (7%)
IF<20 (n=6)	2 (33%)	4 (67%)	0 (0%)

Table 2: CONSORT Compliance, overall and among articles published in higher and lower ranked journals, p=0.07

There was no statistically significant difference in the reporting quality of the 11 subitems, which were added in the checklist after the 2010 revision, among studies published before and after 2010, except for item 23 (registration number and name of trial registry). This item was reported in 3 out of the 11 (27%) pre 2010 studies and in all of the post 2010 studies (100%) (table 3).

Subitems	% of reporting item		P value
	Before 2010 (n=11)	After 2010 (n=9)	
1b	100(11)	100(9)	1.00
3a	36 (4)	66 (6)	0.36
3b	100(11)	100(9)	1.00
6b	100(11)	100(9)	1.00
11b	73 (8)	56 (5)	0.64
13b	64 (7)	89 (8)	0.31
14b	100(11)	100(9)	1.00
17b	27 (3)	33 (3)	1.00
23	27 (3)	100(9)	**0.00**
24	0 (0)	11 (1)	0.45
25	82 (9)	89 (8)	1.00

Table 3 Reporting of CONSORT items in studies published before and after 2010

Discussion

The present study investigated the reporting quality of RCTs assessing infliximab for the treatment of Crohn's disease, using the CONSORT statement 2010. RCTs remain the gold standard for the evaluation of any new intervention and serve as a guidance for an evidence-based decision making in the clinical practice. It is, thus, of outmost importance that their reporting is based upon carefully structured and internationally accepted guidelines, such as the CONSORT statement.

Previous studies assessing the reporting of RCTs in gastroenterology and other medical fields, have indicated suboptimal reporting quality. This study showed an overall adequate compliance of the included publications to the CONSORT statement, as 27 out of the 37 subitems (73%) were clearly reported in >75% of the trials. However, what raises concerns and underlines the need for further amelioration of the reporting of RCTS, is the fact that some of the inadequately reported subitems referred to important methodological parts of

RCTs, such as the trial design (subitem 3a) and the randomization procedure (subitems 8a,9,10). Also items not referring to key methodological features, when incompletely reported can lead to certain types of bias. This was the case with the low reporting of the item 17b (presentation of both absolute and relative effect sizes for binary outcomes), which could result to false estimations of the described effect sizes and lead to misconceptions.

Some of the publishing journals endorsed the CONSORT statement in their writing guidelines. Although this endorsement was irrespective of their impact factor (2 of the high ranked and one of the lower ranked journals endorsed the statement), the analysis indicated a better compliance among the articles published in the higher ranked journals, as it would probably be expected.

The analysis implicated no significant difference in the CONSORT adherence among the studies published before and after the 2010 revision, regarding the subitems that were added to the checklist after 2010. The only subitem being better reported after the introduction of the 2010 version was no23 (registration number and trial registry).

The present study has certain limitations. Firstly, it is a one-reviewer study and thus susceptible to information bias. Additionally, the research procedure has been restricted to pubmed, the most commonly used database. Eligible studies from other sources might have been missed. The only accepted language was English. However, throughout the search there was only one eligible german study that had to be omitted due to the language barrier. Lastly, in the analysis, subitems not applicable to the features of a certain study would be scored as adequately reported. This could have led to an overestimation of the overall trial adherence.

Conclusively, although the majority of the subitems in this study were adequately reported, there were also serious deficiencies regarding important aspects of RCTs. This study finding only emphasizes the need for better reporting quality of RCTS, using tools as the CONORT statement, as this will subsequently be reflected in better quality of the provided medical services.

References

1. https://www.cdc.gov/ibd/IBD-epidemiology.htm
2. https://journals.lww.com/ajg/Fulltext/2018/04000/ACG_Clinical_Guideline__Management_of_Crohn_s.10.aspx
3. https://www.uptodate.com/contents/immune-and-microbial-mechanisms-in-the-pathogenesis-of-inflammatory-bowel-disease?search=crohns%20disease%20pathogenesis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
4. Cottone, M., & Criscuoli, V. (2011). Infliximab to treat Crohn's disease: An update. *Clinical and Experimental Gastroenterology*, *4*(1), 227–238. https://doi.org/10.2147/CEG.S6440
5. http://www.consort-statement.org/
6. Colombel, J. F., Sandborn, W. J., Reinisch, W., Mantzaris, G. J., Kornbluth, A., Rachmilewitz, D., … Rutgeerts, P. (2010). Infliximab, azathioprine, or

combination therapy for Crohn's disease. *New England Journal of Medicine*, *362*(15), 1383–1395. https://doi.org/10.1056/NEJMoa0904492
7. Sands, B. E., Anderson, F. H., Bernstein, C. N., Chey, W. Y., Feagan, B. G., Fedorak, R. N., … Van Deventer, S. J. (2004). Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *New England Journal of Medicine*, *350*(9), 876–885. https://doi.org/10.1056/NEJMoa030815
8. D'Haens, G., Baert, F., Van Assche, G., Caenepeel, P., Vergauwe, P., Tuynman, H., … Donner, A. (2008). for the Belgian Inflammatory Bowel Disease Research Group and the North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet 2008b*, *371*, 660–667. Retrieved from http://scholar.google.com/scholar?q=related:J0b8uKEf-7sJ:scholar.google.com/&hl=en&num=30&as_sdt=0,5%5Cnpapers2://publication/uuid/6F05AFE7-37D9-4A44-90E7-410C192BCB52
9. Regueiro, M., Feagan, B. G., Zou, B., Johanns, J., Blank, M. A., Chevrier, M., … Younes, Z. (2016). Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease after Ileocolonic Resection. *Gastroenterology*, *150*(7), 1568–1578. https://doi.org/10.1053/j.gastro.2016.02.072
10. LÉmann, M., Mary, J. Y., Duclos, B., Veyrac, M., Dupas, J. L., Delchier, J. C., … Colombel, J. F. (2006). Infliximab Plus Azathioprine for Steroid-Dependent Crohn's Disease Patients: A Randomized Placebo-Controlled Trial. *Gastroenterology*, *130*(4), 1054–1061. https://doi.org/10.1053/j.gastro.2006.02.014
11. Ponsioen, C. Y., de Groof, E. J., Eshuis, E. J., Gardenbroek, T. J., Bossuyt, P. M. M., Hart, A., … Morar, P. (2017). Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *The Lancet Gastroenterology and Hepatology*, *2*(11), 785–792. https://doi.org/10.1016/S2468-1253(17)30248-0
12. Regueiro, M., Schraut, W., Baidoo, L., Kip, K. E., Sepulveda, A. R., Pesci, M., … Plevy, S. E. (2009). CLINICAL — ALIMENTARY TRACT Infliximab Prevents Crohn ' s Disease Recurrence After Ileal Resection. *YGAST*, *136*(2), 441-450.e1. https://doi.org/10.1053/j.gastro.2008.10.051
13. Van Assche, G., Magdelaine-Beuzelin, C., D'Haens, G., Baert, F., Noman, M., Vermeire, S., … Rutgeerts, P. (2008). Withdrawal of Immunosuppression in Crohn's Disease Treated With Scheduled Infliximab Maintenance: A Randomized Trial. *Gastroenterology*, *134*(7), 1861–1868. https://doi.org/10.1053/j.gastro.2008.03.004
14. West, R. L., Van Der Woude, C. J., Hansen, B. E., Felt-Bersma, R. J. F., Van Tilburg, A. J. P., Drapers, J. A. G., & Kuipers, E. J. (2004). Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: A double-blind placebo-controlled study. *Alimentary Pharmacology and Therapeutics*, *20*(11–12), 1329–1336. https://doi.org/10.1111/j.1365-2036.2004.02247.x
15. Feagan, B. G., McDonald, J. W. D., Panaccione, R., Enns, R. A., Bernstein, C. N., Ponich, T. P., … Greenberg, G. R. (2014). Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology*, *146*(3), 681-688.e1. https://doi.org/10.1053/j.gastro.2013.11.024
16. Hyams, J., Crandall, W., Kugathasan, S., Griffiths, A., Olson, A., Johanns, J., … Baldassano, R. (2007). Induction and Maintenance Infliximab Therapy for

the Treatment of Moderate-to-Severe Crohn's Disease in Children. *Gastroenterology*, *132*(3), 863–873. https://doi.org/10.1053/j.gastro.2006.12.003
17. Yoshida, K., Fukunaga, K., Ikeuchi, H., Kamikozuru, K., Hida, N., Ohda, Y., … Matsumoto, T. (2012). Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: A 3-year prospective randomized open trial. *Inflammatory Bowel Diseases*, *18*(9), 1617–1623. https://doi.org/10.1002/ibd.21928
18. Ruemmele, F. M., Lachaux, A., Cézard, J. P., Morali, A., Maurage, C., Giniès, J. L., … Sarles, J. (2009). Efficacy of infliximab in pediatric Crohn's disease: A randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. *Inflammatory Bowel Diseases*, *15*(3), 388–394. https://doi.org/10.1002/ibd.20788
19. Fukushima, K., Sugita, A., Futami, K., Takahashi, K. I., Motoya, S., Kimura, H., … Suzuki, Y. (2018). Postoperative therapy with infliximab for crohn's disease: A 2-year prospective randomized multicenter study in japan. *Surgery Today*, *48*(6), 584–590. https://doi.org/10.1007/s00595-018-1627-x
20. Farrell, R. J., Alsahli, M., Jeen, Y. T., Falchuk, K. R., Peppercorn, M. A., & Michetti, P. (2003). Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: A randomized controlled trial. *Gastroenterology*, *124*(4), 917–924. https://doi.org/10.1053/gast.2003.50145
21. Steenholdt, C., Brynskov, J., Thomsen, O. O., Munck, L. K., Christensen, L. A., Pedersen, G., … Ainsworth, M. A. (2015). Implications of infliximab treatment failure and influence of personalized treatment on patient-reported health-related quality of life and productivity outcomes in crohn's disease. *Journal of Crohn's and Colitis*, *9*(11), 1032–1042. https://doi.org/10.1093/ecco-jcc/jjv139
22. Vande Casteele, N., Ferrante, M., Van Assche, G., Ballet, V., Compernolle, G., Van Steen, K., … Vermeire, S. (2015). Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*, *148*(7), 1320-1329.e3. https://doi.org/10.1053/j.gastro.2015.02.031
23. D'Haens, G., Vermeire, S., Lambrecht, G., Baert, F., Bossuyt, P., Pariente, B., … Williams, S. (2018). Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. *Gastroenterology*, *154*(5), 1343-1351.e1. https://doi.org/10.1053/j.gastro.2018.01.004
24. Kierkuś, J., Iwańczak, B., Wegner, A., Dadalski, M., Grzybowska-Chlebowczyk, U., Łazowska, I., … Sładek, M. (2015). Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. *Journal of Pediatric Gastroenterology and Nutrition*, *60*(5), 580–585. https://doi.org/10.1097/MPG.0000000000000684
25. Arvanitaki, A. D., Mantzouratou, P., & Zintzaras, E. (2017). Assessing the reporting quality of randomized-controlled clinical trials involving novel oral anticoagulants in patients with atrial fibrillation based on the CONSORT statement. *International Journal of Clinical Trials*, *4*(4), 147. https://doi.org/10.18203/2349-3259.ijct20174862