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Μεταπτυχιακή εργασία με τίτλο:

«Assess the reporting quality of randomized-controlled trials in multiple sclerosis from 2000 to 2015, based on CONSORT statement»

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Assess the reporting quality of randomized-controlled trials in multiple sclerosis from 2000 to 2015, based on CONSORT statement

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PURPOSE: Randomized controlled trials (RCTs) are the best tool to evaluate the effectiveness of clinical interventions. The CONSORT (Consolidated Standards of Reporting Trials) statement is an evidence based approach to improve the quality of reporting of RCTs. The aim of this study was to evaluate the reporting quality of published RCTs concerning multiple sclerosis from 2000 to 2015 according to a checklist based on the CONSORT statement.

METHODS: PubMed was searched for English-language RCTs involving patients with multiple sclerosis (MS). Trials were considered eligible when participants were randomly assigned to at least two medicinal treatment arms and included patients with MS. Quality of reporting was assessed using a 39–item questionnaire based on the CONSORT checklist. Articles were grouped in three 5-year periods and comparisons were made using descriptive statistics.

RESULTS: The search identified 75 eligible articles for analysis. 20 of the 38 items of the checklist were addressed in 75% or more of the studies. Reporting of more than 75% of CONSORT items was increased during the three equal time periods from 2000 to 2015 ($p<0.05$).

CONCLUSIONS: Quality of reporting in RCTs focusing on multiple sclerosis is showing improvement over time but remains unsatisfactory. Further improvement of reporting is necessary to assess the validity of clinical research

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Abbreviations and Acronyms

RCT = randomized controlled trial
CONSORT = Consolidated Standards of Reporting Trials
ITT = intention-to-treat
MS = Multiple Sclerosis
RRMS = Relapsing Remitting MS
SPMS = Secondary Progressive MS
PPMS = Primary Progressive MS
CIS = Clinically Isolated Syndrome

INTRODUCTION

The publication of scientific research results and reporting of biomedical information are linked with the development of clinical therapeutic trials. The highest rank within the clinical studies is occupied by the randomized controlled trials (RCT) which consider to be "the most powerful tool in modern clinical research"(1). RCTs represent a key research activity with the potential to improve the quality of health care and control costs through careful comparison of alternative treatments or placebo (2). This happens mainly because the act of randomizing patients to receive or not receive the intervention ensures that, on average, all other possible causes are equal between the two groups. Thus, any significant differences between groups in the outcome event can be attributed to the intervention and not to some other unidentified factor (3). However, the overwhelming amount of information available in biomedical journals during the past 50 years has created problems in a variety of areas, such as publication or selection bias (4, 5). Readers need to know the quality of the trials, in order to assess the strengths and limitations of RCTs (6, 7). In addition, healthcare providers depend upon the reporting of methodological factors in the reports of RCTs to allow them to determine the validity of the trials upon which they base their clinical practice and their treatment guidelines (8, 9).

It is clear that the evaluation of the quality of randomized controlled trials (RCTs) is central to evidence-based health care. Important methodologic detail may, however, be omitted from published reports, and the quality of reporting is therefore often used as a proxy measure for quality (10). A well conducted but badly reported trial will be misclassified and a general, unclear and inaccurate reporting may reflect faulty methods (7, 11, 12). Additionally since pharmaceutical industry is the major funder of trials, information on funding sources and the role of the industry is also essential.

An overwhelming body of evidence stating that the completeness of reporting of randomized controlled trials (RCTs) is not optimal has accrued over time. In the mid-1990s, in response to these concerns, an international group of clinical trialists, statisticians, epidemiologists, and biomedical journal editors developed the CONsolidated Standards Of Reporting Trials (CONSORT) Statement. The CONSORT Statement, most recently updated in March 2010, is an evidence-based minimum set of recommendations including a checklist and flow diagram for reporting RCTs and is intended to facilitate the complete and transparent reporting of trials and aid their critical appraisal and interpretation (13). CONSORT urges completeness, clarity, and transparency of reporting, which simply reflects the actual trial design and conduct (14). However, the CONSORT statement should not be used as a quality appraisal tool but rather as a guide for reporting of RCTs.

A number of publications have studied the quality of reports of RCTs in subspecialties of medicine (15-20). In 2012 a review of the quality of reports in multiple sclerosis was also published including 53 articles from five leading medical journals from 1993 to 2010 (21).

Multiple sclerosis is one of the most common autoimmune disorders affecting the CNS (22) with yet unsatisfactory explanation of pathophysiology and inadequate treatment making good quality trials a necessity.

In this study we analyzed the quality of reporting of Randomized Controlled Trials involving patients with Multiple Sclerosis (Relapsing Remitting MS, Primary Progressive MS, Secondary Progressive MS, Clinically Isolated Syndrome and first demyelinating event suggestive of MS) using the items of the revised CONSORT 2010 statement checklist (14) with an additional item.

METHODS

Data Sources and Search Strategies

We searched PubMed (1st of January 2000 to 15th of July 2015) for reports on RCTs involving patients with MS. As a search criterion the phrase "Multiple Sclerosis" was used. We used as filters the "Randomized Controlled Trial" type of article, "English" language and "Humans" for species.

Eligibility of Studies

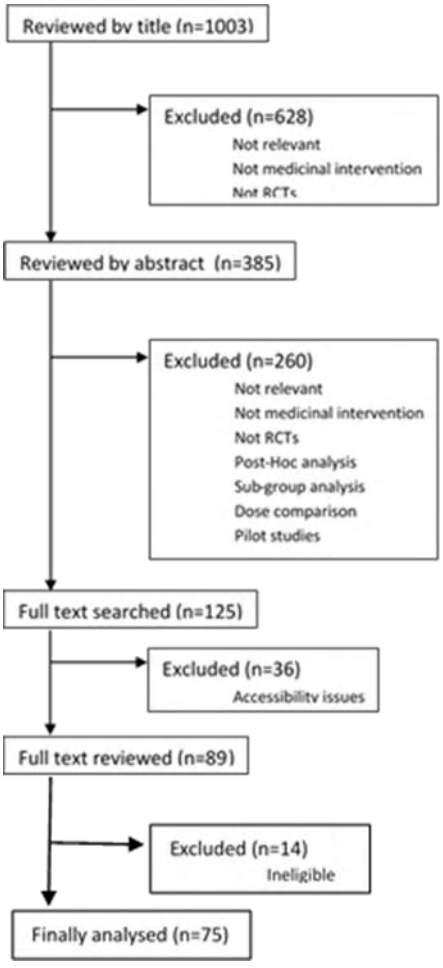
Trials were eligible if they had randomly assigned participants to at least two medicinal treatment arms and included patients with MS including all different types of the disease (Relapsing Remitting MS, Primary Progressive MS, Secondary Progressive MS, Clinically Isolated Syndrome and first demyelinating event suggestive of MS). Reports of trials on MS symptoms treatments, non-medicinal treatments, dose comparison studies, small pilot studies and any article with information resulting from a previous conducted trial (post-hoc analysis, sub-group analysis, sub-studies) where excluded.

Reporting Assessment Tool

As assessment tool for reporting quality we used the revised CONSORT 2010 checklist (http://www.consort-statement.org) which is a 25-item checklist with sub-items (total 37 items) in which we added an additional item (No 13) when an article included or not a participant flow diagram. There was no training of the reviewer on the CONSORT use. As guidelines the CONSORT explanation and elaboration document (available at the CONSORT web page) was used. From the total of 75 eligible trials 40 were conducted before 2010 when the revise CONSORT version was published and 35 after 2010. We used the revised version for all of the articles. The full CONSORT checklist can be found at the Appendix.

Evaluation - Analysis

Evaluation was made using the Microsoft Excel 2010 software. During the evaluation the following procedures were followed: a. all items were investigated in terms of whether they reported, not actually carried out during the trial b. when an item was reported in a different section of the trial (title, abstract, methods, results, discussion) it was considered as a negative response except of the information on "other information" section which was considered as positive regardless where it was mentioned c. alternative responses (apart of yes or no) or unclear responses to each question were coded as negative responses. We separated the articles in three five-year time periods. From 2000 to 2004. From 2005 to 2009 and from 2010 to 2015. We also separated the reporting items into five groups. 1. Title/Abstract and Introduction 2. Methods 3. Results 4. Discussion 5. Other information.
We calculated the greater than 75% (>75%) compliance with the checklist, meaning the percentage of the articles (overall and by time period) that reported at least 75% of the 38 checklist items. We also calculated the percentage of the items that was reported in at least 75% of the articles in overall and by item group (title and abstract, methods, results, discussion, other) for the 15 year period and by 5-year period. Comparison between >75% compliance among different time periods was made using the chi-square statistic for a 2x3 table (SPSS v.21 software).
Web search, review, evaluation and statistics was made by the author.



RESULTS

Eligible studies

The process was made in four steps. PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) using the criteria mentioned in methods, returned 1003 related articles which were reviewed by title. 628 were excluded because they were not relevant or had a non medicinal intervention (behavioral treatment, exercise, herbal) or were not randomized trials. The 385 articles left reviewed by abstract and 260 excluded for the same reasons. 125 articles searched for full text from which 36 were not found due to accessibility reasons. Finally 89 full text articles reviewed from which 14 excluded. 75 articles finally were evaluated including a total of 6150 randomized patients. A list with these 75 articles can be found at the Appendix.

Main Results

Of a total of 75 articles, 12 were published the period 2000-2004, 28 the period 2005-2009 and 35 the period 2010-2015. The percentages of articles reporting each item by publishing period is shown at Table 1. 20 checklist items (52.6%) were reported from 75% or more of the articles published from 2000 to 2015, 17 (44.7%) the period 2000 to 2004, 19 (50%) the period 2005 to 2009 and 24 (63.2) the period 2010 to 2015 showing a trend of increase in reporting CONSORT items after its revision. The numbers and percentages showing the checklist items that was reported by 75% or more of the articles by period and by group is shown at Table 2 and Figure 1. Most of the items showed an increase in reporting during time.

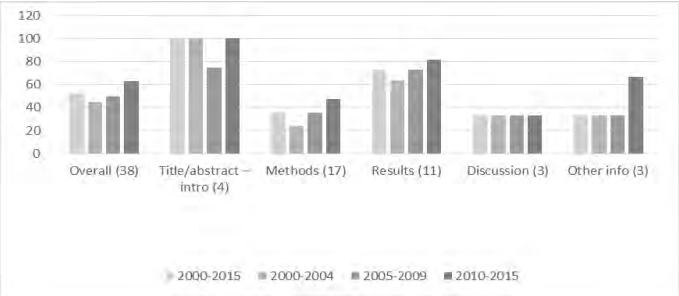


Figure 1 Percentage of items reported in >75% of the articles by period and by group

The >75% compliance with CONSORT by time period was: overall: 22 (29.33%), 2000-2004: 1(8.33%), 2005-2009: 6 (21.42%), 2010-2015: 15 (42.85) expressing a statistical significant difference in compliance among the different time periods (p-value= 0.039)

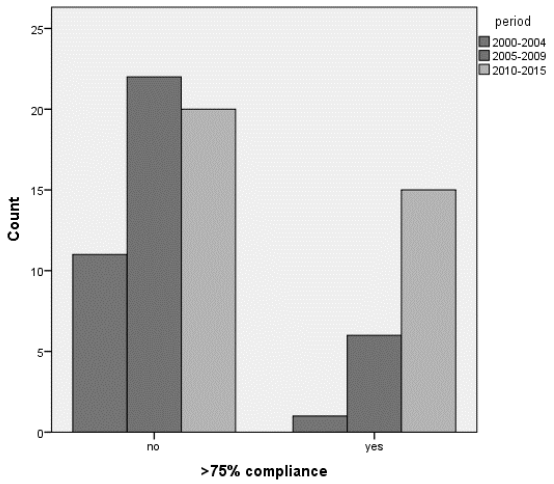


Figure 2 Bar chart of >75% compliance of trials with the CONSORT checklist

DISCUSSION

This study show that reporting of RCTs in Multiple Sclerosis is still not optimal according to the CONSORT statement. Some of the reporting items are underreported. Some of them are not critical for the evaluation of the quality of the RCT like the item 3b (Important changes to methods after trial commencement, with reasons), 7b (explanation of any interim analyses and stopping guidelines) and 14b (why the trial ended or was stopped) which are mentioned only when applicable. Other items are important methodological techniques which should always be reported, like: item 8a (method used to generate the random allocation sequence) reported in 57% of the articles and item 9 (Mechanism to implement the random allocation sequence describing any steps taken to conceal the sequence until interventions were assigned) reported in 28% of the articles. Item 24 (where the full trial protocol can be accessed, if

Table 1. Proportion of reporting of 38 items in a total of 75 RCTs in MS by publication period

Data item	Combined 2000-2015 n=75 *	2000-2004 n=12	2005-2009 n=28	2010-2015 n=35
ABSTRACT / TITLE				
1a	0,77	0,92	0,61	0,86
1b	0,81	0,75	0,79	0,86
INTRODUCTION				
2a	1,00	1,00	1,00	1,00
2b	0,88	0,92	0,82	0,91
METHODS				
3a	0,87	0,67	0,89	0,91
3b	0,05	0,17	0,00	0,06
4a	0,89	0,92	0,79	0,97
4b	0,59	0,58	0,46	0,69
5	0,99	1,00	0,96	1,00
6a	0,96	1,00	0,93	0,97
6b	0,05	0,08	0,00	0,09
7a	0,65	0,58	0,54	0,77
7b	0,19	0,08	0,18	0,23
8a	0,57	0,42	0,54	0,66
8b	0,71	0,50	0,68	0,80
9	0,28	0,00	0,21	0,43
10	0,37	0,17	0,32	0,49
11a	0,64	0,42	0,61	0,74
11b	0,31	0,17	0,32	0,34
12a	0,96	0,92	0,93	1,00
12b	0,85	0,67	0,82	0,94
RESULTS				
13	0,85	0,75	0,79	0,94
13a	0,93	1,00	0,89	0,94
13b	0,88	0,83	0,86	0,91
14a	0,47	0,33	0,50	0,49
14b	0,09	0,17	0,04	0,11
15	0,97	1,00	0,96	0,97
16	0,91	0,83	0,89	0,94
17a	0,91	0,83	0,93	0,91
17b	0,73	0,50	0,75	0,80
18	0,76	0,75	0,68	0,83
19	0,83	0,58	0,75	0,97
DISCUSSION				
20	0,64	0,58	0,64	0,66
21	0,59	0,67	0,46	0,66
22	0,99	1,00	1,00	0,97
OTHER INFO				
23	0,53	0,00	0,32	0,89
24	0,03	0,00	0,00	0,06
25	0,87	0,83	0,79	0,94

** 1 Percentage of articles reporting the item*

available) is the most underreported item, but it's a new entry in the CONSORT 2010 checklist. It is not reported in any article the two periods from 2000-2009 and in the 6% of the articles the period 2010-2015 showing a slow increase in compliance with the CONSORT.

Table 2 Numbers and percentages of items reported by 75% or more of the articles by reporting group

Checklist items / period	2000-2015 N(%)	2000-2004 N(%)	2005-2009 N(%)	2010-2015 N(%)
Overall (38)	20 (52.6)	17 (44.7)	19 (50)	24 (63.2)
Title/abstract – intro (4)	4 (100)	4 (100)	3 (75)	4 (100)
Methods (17)	6 (35.3)	4 (23.5)	6 (35.3)	8 (47.1)
Results (11)	8 (72.7)	7 (63.6)	8 (72.7)	9 (81.8)
Discussion (3)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)
Other info (3)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)

Although the quality of reporting is not optimal most of the items were reported in more articles at every time period indicating an improvement of reporting over time.

This study was not designed to evaluate the impact of the quality of the journal on the quality of reporting. It is our belief though that journals with greater Impact Factor are promoting a better and more "CONSORT-compliant" way of reporting.

In 2012 Signori et al. (21) in his review of the quality of reporting of RCTs (from 1993 to 2010) found some similar data. The identification of the trial as randomized in the title was 49.1% and we found it 77%. Similarly the allocation concealment method was reported as 17% (here 28%). The primary outcome definition founded similar to our results at 96.2% (here 96%). These data are enhancing the notion of improvement in reporting quality over time.

This study has its weaknesses. We used the revise CONSORT 2010 checklist for all the trials despite they were published before or after its publication. The search of trials and the review was made by only one person decreasing the validity of the procedure.

In conclusion, our attempt to assess the quality of RCTs, centering on Multiple Sclerosis, indicated an improvement of reporting of RCTs by time period. In the area of Multiple Sclerosis research, which is still searching for an effective treatment, further improving the quality of RCTs and their reporting could assist health care providers to their clinical decisions, increase the clinical significance of RCTs, and direct more specifically future medical research.

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APPENDIX

CONSORT CHECKLIST (14)

Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses

Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

LIST OF ARTICLES

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