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Master's Thesis:

Evaluation of the reporting quality of Randomized Controlled Trials for treatments in Multiple Myeloma published the last 5 years using the CONSORT 2010 statement

"Αξιολόγηση της πληρότητας των παρεχόμενων στοιχείων των Τυχαιοποιημένων Κλινικών Δοκιμών για θεραπείες στο Πολλαπλούν Μυέλωμα που έχουν δημοσιευθεί τα τελευταία 5 χρόνια, χρησιμοποιώντας τη δήλωση CONSORT"

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Outline

Evaluation of the reporting quality of Randomized Controlled Trials for treatments in Multiple Myeloma published the last 5 years using the CONSORT 2010 statement.

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Abstract

INTRODUCTION: Randomized Controlled Trials (RCTs) are the best tool to evaluate the effectiveness of clinical interventions. The Consolidated Standards of Reporting Trials (CONSORT) statement first introduced in 1996 and revised twice to its current form in 2010, is an evidence based approach to improve the reporting of randomized controlled trials.

OBJECTIVE: Purpose of this study is to evaluate the completeness of reporting of RCTs published the last 5 years (from May 2011 to May 2016), testing therapeutic interventions for patients with Multiple Myeloma.

METHODS: The electronic database PubMed was screened for RCTs, punished in English the last 5 years, examining therapies for patients with Multiple Myeloma. Trials were considered eligible when participants were randomly assigned to at least two treatment arms. Completeness of reporting was assessed using the 2010 CONSORT checklist, which consists of 25 items with sub-items (37 items in total). Response alternatives to each item in the checklist were: yes, no and not applicable. Primary end-point was the evaluation of the completeness of reporting of RCTs as measured by adequate or inadequate reporting of the 25 items on the 2010 Consort checklist. Secondary end-points included comparison of quality of reporting by year from 2011 to 2016, correlation of reporting with Impact Factor and number of Randomized Participants, as well as a sub-group analysis which compared the quality of reporting of 5 CONSORT items (7a, 8a, 8b, 9, 16), which are considered to be "key methodological factors", between two time periods (May 2011-2013 & 2014-May 2016).

RESULTS: The search identified 55 eligible articles for analysis. Overall compliance was 63,10%. Only 15 out of the 55 (27,3%) articles reported at least 75% of the checklist items, while only 14 out of the 37 items were reported in 75% or more of the articles. No significant improvement in the reporting quality of the articles over time was found. Correlations were found to be significant but after adjusted for co-factors the significance was lost, whereas a statistical significant difference ($p<0,05$) was found in the reporting of "5 key methodological factors" during the two time periods.

Conclusions: Completeness of reporting in RCTs focusing on patients with MM still remains unsatisfactory and no clear evidence of improvement over time was found in our study. These results suggest that further actions should be taken by authors, reviewers, and editors, since inadequate reporting makes the interpretation of RCTs difficult if not impossible.

INTRODUCTION

Randomized Clinical Trials

The dissemination of biomedical information and publication of research results is integral to scientific endeavor and is closely linked with the historical development of the clinical trial [1]. Clinical trials come in all shapes and sizes, and the randomized controlled trial (RCT) resides within the hierarchy of clinical studies. In the 1970s, the FDA in the United States of America, passed mandate title 21, requiring an RCT before a drug can be approved for sale.[5] Nowadays the randomized controlled trial sets the methodological standard of excellence in medical research and is widely accepted as the ''gold standard'' by which the benefit of a pharmaceutical intervention is judged [2]. The reason why RCTs are considered the gold standard for establishing effectiveness is because they minimize bias in

evaluating new treatment strategies [1, 4]. The unique capability of randomized controlled trials to reduce bias depends on investigators being able to implement their principal bias reducing technique—randomization [2].

The randomized controlled trial is one of the simplest but most powerful tools of research. In essence, the randomized controlled trial is a study in which people are allocated at random to receive one of several clinical interventions [3, 6]. Random assignment has been successfully used for over 55 years and is now the preferred method for determining the merits of interventions [5, 10].

R A. Fisher[11] firstly developed randomization as a basic principle of experimental design in the 1920s, and used the technique predominantly in agricultural research. The successful adaptation of randomized controlled trials to health care took place in the late 1940s, largely because of the advocacy and developmental work of Sir Austin Bradford Hill [16]. His efforts culminated in the first experimental [13] and published [9] use of random numbers to allocate trial participants. The Medical Research Council trials on streptomycin for pulmonary tuberculosis are rightly regarded as a landmark that ushered in a new era of medicine [2, 9]. Soon after, randomization emerged as a crucial technique in securing unbiased comparison groups and the methodology of the randomized controlled trial has been increasingly accepted while the number of randomized controlled trials reported has grown exponentially. [2, 3]

If complete matching could be achieved, the testing of therapies would be easier. However, the marked variability of human responses to both diseases and treatments and the realities of observer error and bias make proper matching impossible to attain. For this reason randomization is recognized as the best available technique of approximating the equality of patient groups being compared [14]. Randomization is a procedure that allows for chance allocation of trial participants to the treatment groups. The procedure in principle ensures that treatment groups are balanced in terms of baseline characteristics and thus any significant differences between groups in the outcome event can be attributed to the intervention and not to some other unidentified factor, thereby providing the basis for crude between-group comparison of treatment effect [7].

According to Hill who stressed the objectivity of randomization: *"having used a random allocation, the sternest critic is unable to say when we eventually dash into print that quite probably the groups were differentially biased through our predilections or through our stupidity"*. [15, 16]

The successful implementation of this all-important procedure, as was observed by previous authors [2] depends on two main procedures:

1) generation of an unpredictable random allocation sequence and
2) concealment of that sequence until assignment occurs. [3,7]

Evidence Of Bias

Though randomized controlled trials are widely agreed to yield the most reliable scientific information, careless or inappropriate analysis may lead to misleading conclusions [19]. An 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 [24, 25]

The validity of an RCT depends on the correct performance of a large number of essential steps. Unless all these steps are accurately accounted for and described, critical clinicians cannot know what actually took place, cannot judge whether the conclusions drawn by the authors are justified, and cannot judge whether their patients are likely to be helped or harmed by the intervention [17]. Reports of RCTs should provide readers with adequate information about what went on in the design, execution, analysis, and interpretation of the trial. Such reports will help readers judge the validity of the trial [18].

Evidence produced repeatedly over the last 30 years indicates a wide chasm between what a trial should report and what is actually published in the literature. [21]

Even from the 1980s Fr. Mosteller & Colleagues [22] in a survey of controlled trials in cancer noticed deficiencies in current reporting standards of that period and stressed out that published articles do not give readers essential information needed to judge a trial's methodological strengths. Unless such details are reported, readers cannot adequately assess the confidence a trial's results deserve [22]. The features, Mosteller & Colleagues, looked for in their review were reports of 1) how randomization was carried out, 2) P-values, that is, explaining the statistics used, 3) survival curves, 4) blindness in the trial, 5) power and sample size, and 6) informed consent. The reason for selecting the above mentioned features is that beyond their importance, these features have the advantage of ease of recognition in a report or an explanation. Finally they argued that: *"Certain features could not have been implemented in some of these studies, in others they clearly could have been. However, as readers, we were not always in a position to evaluate when a feature could or could not have been implemented in each comparison"* [22]. Or to put it differently, in interpreting trial results, the reader has only the published paper on which to rely on [14].

In the same article Mosteller et al [22] points out that only 3 out of the 19 clinical trials in the Myeloma and Leukemia group that they reviewed reported the method of randomization, he continues saying that *"especially if the method is not reported, the skeptic must be allowed doubts about the effectiveness of the method used. Not only must the randomization be well done, but it is best if it can be checked on later, should questions arise, as they frequently do"*. In conclusion Mosteller et al recommended that in order encourage authors to include the appropriate descriptions, the editor should provide a checklist of items expected to be published in a report on a clinical trial [22].

In 1983, Chalmers and colleagues [26] found that trials in which the allocation schedule had been inadequately concealed yielded larger estimates of treatment effects than trials in which allocation had been adequately concealed [20]. Later Schulz and colleagues have shown empirically that in comparison with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (i.e. did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects (P<.001), while odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials [20]. One possible interpretation is that some trials with inadequate reporting of allocation concealment actually had faulty randomization, and faulty randomization allowed the introduction of bias [21].

In separate reviews of medical journals concerning the adequacy of randomization procedures in trials, studies [2] & [25] respectively found 129/206 (63%) and 79/232 (34%) of authors did not specify the method used to generate an allocation sequence, despite the presence of a "*Consolidated Standard of Reporting Trials*" (CONSORT) [10] statement that stipulated that authors should make clear how randomization was conducted. The result of these reviews also shows that non-random methods such as using case record number, date of birth and date of presentation are still being confused and presented as a random method by some researchers. Therefore we can reach the conclusion that non-reporting of the allocation technique in some controlled clinical studies could be because the methods used by the authors of such studies were short of a true random process [7]

CONSORT

In response to overwhelming evidence and consequences of poor–quality reporting of RCTs, the Consolidated Standards of Reporting Trials (CONSORT) statement came about because of the need to provide readers with enough valid and meaningful information concerning the design, conduct, and analysis of RCTs [21].

The first step was made when JAMA published in December 1994 the Standards of Reporting Trials (SORT) statement. The authors of the SORT statement defined structured reporting as "providing sufficiently detailed information about the design, conduct and analysis of the trial for the reader to have confidence that the report is an accurate reflection of what occurred during the various stages of the trial" and proposed 32 items for inclusion in a checklist to be used when preparing a report of an RCT. [18]

Independently, approximately 5 months later (March 14 to 16, 1994), another group, the "Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature", met to discuss similar challenges facing the reporting of clinical trials. Their proposal consisted of a checklist of items that should be included when reporting a clinical trial, along with a suggestion that editors add it to the "Instructions for Authors" section[21]. A subsequent Editorial [17] urged both groups to meet and decide which recommendations from each group's proposal should be retained. This meeting resulted in the ***Consolidated Standards of Reporting Trials (CONSORT) statement of 1996****, which consists of a checklist of 21 items along with a flow diagram that pertain mainly to the methods, results and discussion of an RCT report and identify key pieces of information necessary to evaluate the internal and external validity of the report [21].*

The original Consort statement has been revised twice so far. The first revision was in 2001 [10, 27, 28] and thereafter updated to its current version in 2010 [29]. The 2010 CONSORT statement comprises of a 25 items' checklist along with a flow diagram documenting the flow of participants through RCTs. It provides guidance for reporting all randomized controlled trials, but focuses on the most common design type, which are the "individually randomized, two group, parallel trials"[29]. Since its publication in 1996 the consort statement has been widely supported, it has been translated into 13 languages [30] while there are currently 585 biomedical journals worldwide that endorse the CONSORT statement [31].

The CONSORT statement has evolved as evidence based approach to improve the quality of reports of RCTs, enabling readers to understand their conducts and to gauge the validity of their results [32]. Diligent adherence by authors to the checklist items facilitates clarity, completeness, and transparency of reporting [29]. Providing reporting quality could be used as a proxy measure for methodological quality [33]. This could be justified if the assumption were correct that faulty reporting reflects faulty methods [34] However, even if the quality of reporting does not reflect absolutely the quality of the research and the adequacy of the methods, it is well accepted that unclear and inaccurate reporting reflects faulty methods, while a well-conducted but badly reported trial will be misclassified [20, 8, 34]. It is justified to say that the thorough use of the CONSORT guidelines affects trials' quality, since it can indirectly affect their design and conduct. Transparent reporting can reveal deficiencies in research if they exist. Thus, investigators who conduct inadequate trials, but who must transparently report, should not be able to pass through the publication process without revelation of their trial's inadequacies. That emerging reality should provide impetus to improved trial design and conduct in the future. Taking into account all of the above, the CONSORT statement should not be used as a quality appraisal tool but rather as a guide for reporting of RCTs [33].

As such, while the CONSORT Statement is widely endorsed, there is huge variation in terms of how CONSORT policies are implemented [35]. A number of publications have studied the quality of reports of RCTs in subspecialties of medicine [4, 5, 32, 36, 37, 38, 39, 40, 45] in the recent years. Among these subspecialties the Hematology field and Multiple Myeloma disorder in particular hasn't escaped without judgment of the reporting quality of its published clinical trials.

Multiple Myeloma

Multiple myeloma (MM) is a neoplastic plasma cell disorder. Plasma cell neoplasms have proven challenging to classify in a biologically correct and clinically useful way [43]. According to WHO classification of 2008 other clinical entities that fall into the same plasma cell neoplasms category as MM are: Monoclonal gammopathy of undetermined significance (MGUS), plasma cell myeloma (asymptomatic/smouldering myeloma, non-secretory myeloma, plasma cell leukemia), plasmatocytoma, Immunoglobulin deposition diseases and osteosclerotic myeloma (POEMS syndrome)[12].

MM is a disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow, and usually monoclonal protein in the blood and/or urine. It is associated with end-organ damage consisting of the CRAB criteria (anaemia, renal insufficiency, bone lesions and/or hypercalcaemia). It is the second most frequent haematological neoplastic disease after non-Hodgkin lymphoma and comprises 1% of all cancers and 10% of haematological malignancies. It primarily affects older individuals; the median age at the time of diagnosis is 70 years, and two-thirds of MM patients are over 65 years of age when first diagnosed [41, 42].

There are a number of strategies for management of patients with multiple myeloma, and decisions are based on a variety of factors including patient factors such as age, end-organ function, and cytogenetics. At this time induction therapy is given to most patients with active disease and may include corticosteroids, cytotoxic agents, immunomodulating agents, proteasome inhibitors, or a combination of these agents [44]. Patients according to their age and co-morbidities are broadly subdivided into two categories, those who are able to undergo stem cell transplantation and those who are ineligible for transplantation. Patients who are eligible for high-dose chemotherapy followed by stem cell transplantation often proceed to autologous stem cell transplantation (ASCT) following induction therapy, while patients who are not considered “fit” for transplantation are treated with treatment strategies utilizing a variety of anti-myeloma drugs. Over the last decade, along with the conventional chemotherapy (melphalan etc), numerous drug therapies have emerged for the treatment of multiple myeloma including immunomodulating agents (namely thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (namely bortezomib and carfilzomib) and monoclonal antibodies, such as daratumumab (anti-CD38). Although a hope was expressed in the early years of their discovery that with the new agents the need for ASCT for younger and fit patients would be diminished, the usefulness of ASCT remains still today unquestionable according to recently published RCTs[47]. Nonetheless these agents have transformed the treatment of multiple myeloma and the role of high-dose chemotherapy followed by stem cell transplantation in the treatment of the disease [44].

Finally it is not wrong to say that MM is a complicated clinical entity which requires sophisticated multimodal interventions and treatment schedules. Almost all major therapeutic advances and treatment strategies for this disease have occurred as a result of RCTs.

In 2001 a review, which critically appraised therapeutic innovations tested in RCTs from 1966 to 1998 for Multiple Myeloma patients, was published. That particular review assessed RCTs in terms of quality dimensions of design, conduct, analysis and reporting [4]. However, no other study to our knowledge has assessed the quality of reporting of RCTs, focusing on patients with MM, using the items of the revised 2010 CONSORT statement.

In the present study, we analyzed the quality of reporting of RCTs involving treatments of patients with Multiple Myeloma, using the items of the revised 2010 COSORT statement [29]. The period covered by this report is the last 5 years (from May 2011 to May 2016).

METHODS

Search Stretegies

Literature for this review was systematically identified by screening the electronic database "PubMed" for reports on RCTs involving patients with MM published the last 5 years (with starting point the date when we made our search, "between May 2011 and May 2016"). The search criterion we used was "Multiple Myeloma" and the restrictive filters we used were: "Clinical Trial" for the article type, "English" for language, "Human" for species and "5 years" for publication dates.

Study Identification

References were screened by one researcher (NP) for eligibility in the study. Trials were eligible if they had randomly assigned participants to at least two treatment arms and included patients with MM comprising also of clinical entities related to multiple myeloma that fall into the same category of "plasma cell neoplasms" (MGUS, plasma cell myeloma, plasmatocytoma, Immunoglobulin deposition diseases and osteosclerotic myeloma). We looked for the terms "random", "randomized" and "randomization" as an indicator of the way/method by which participants were assigned to treatment groups. To be included in the study, RCTs must have randomized human subjects into two or more "**therapeutic**" interventions, while RCTs evaluating diagnostic strategies were excluded. Reports of trials regarding treating symptoms of MM or coping with side effects were excluded. Also all observational studies, reviews, small pilot studies, meta-analysis and pooled analysis of RCTS, as well as short communications, editorials, non-patient RCTs and any article with information resulting from a previous conducted trial (post-hoc analysis, sub-group analysis, sub-studies) were excluded.

Reporting assessment tool

As assessment tool for reporting quality we used the revised CONSORT 2010 checklist which can be found through the CONSORT- website (http://www.consort-statement.org). This checklist comprises of a 25-item checklist with sub-items (37 items in total), that provide guidance in reporting randomized controlled trials. As guidelines we used "the CONSORT explanation and elaboration document" (available at the CONSORT web page) [46]. Although all items in the CONSORT checklist are considered important as to improve the quality of reporting of RCTs, some are more subjective than others [40]. A variety of other studies have identified a number of methodological factors as necessary items that can judge the internal validity of RCTs [4, 20, 26, 40, 48, 49]. After identifying the most common items reported by these studies, emphasis was placed in examining the ***5*** mostly cited "*key methodological factors"* that are also included in the 2010 CONSORT statement. These items, which can and should be implemented in each and every complete randomized trial, have been shown to bias outcomes, and included details about: sequence generation, allocation concealment, randomization implementing method, justification of sample size, and whether the analysis was done by original assigned groups (intention to treat analysis) along with the number of participants for each group included in each analysis {CONSORT 2010 items (7a, 8a, 8b, 9, 16)}.

Evaluation & analysis of outcomes

The primary outcome of this study is the evaluation of the completeness of reporting of RCTs as measured by adequate or inadequate reporting of the 25 items on the 2010 Consort checklist. The procedures followed to achieve this goal are outlined bellow: 1) The items in the checklist were investigated in terms of whether they were reported or not. No assessment was made on the quality of what was reported or if they were actually carried out during the trial. 2) Response alternatives to each item in the checklist originally were: yes, no, unclear, and not applicable. Not-applicable responses were coded as missing data. However during the course of this study we noticed that what constitutes 'complete' reporting for each checklist item appeared to be variable between evaluations, depending on author's interpretation. A review by Turner et al on the completeness of reporting of RCTs recommended that future evaluations assess the completeness of reporting of each checklist item in a dichotomous fashion (i.e. 'complete' versus 'incomplete') and moreover generally suggested to trial authors that items are only 'complete' when adhered to in their entirety. After all it is the intention of the CONSORT group that all concepts contained within an individual checklist item to be reported in

order to be considered adequately (or completely) reported [35]. For the reasons mentioned above we revised our methods and thus when evaluations used more than two categories to judge adherence to a given checklist item, we collapsed them to create a dichotomous value between adequately or inadequately reported RCTs, which is translated to the reporting or non-reporting of a checklist item. For instance, when an item was judged as 'partially' reported, it was considered 'inadequate' i.e. not-reported. **So each applicable item in the CONSORT checklist entails a YES or NO response option**. An item was graded a score of "one"= YES, if there was a statement describing the item and clear description of the method used was required to define the adequacy of the assessed component. If no description of the item was included, the item would be graded a score of "zero"= NO. Omission or unclear information were equated to inadequate reporting quality and were graded a score of "zero". When an item was non-applicable to a certain RCT it was considered as missing data and was not accounted for in the calculation of the results (it was omitted both from the numerator and the denominator). 3) It didn't matter whether an item was reported in a different section of the trial, "it is not the intention of the CONSORT group to standardize the structure of reporting, authors should simply address checklist items somewhere in the article, with ample detail and lucidity [29]", with an exception for the items that were reported only in the abstract and not the full paper. If a checklist item that is supposed to be reported in the main article but was found only in the abstract it received a negative response (e.g. item 23 "registration number and name of trial registry was frequently reported in the abstract but not in the main article). 4) For items which in a first glance received a negative response, but in the article were clearly referred to in the "appendix" or the "supplementary data" for more information, then we would examine the reference and if the item was adequately reported it could entail a positive response. An exception to this rule was made for the item 8a-"method used to generate the random allocation sequence", where the CONSORT Explanation and Elaboration Document specifically states that "it is important that information on the process of randomization is included in the body of the main article and not as a separate supplementary file; where it can be missed by the reader" [46].

For secondary outcomes in addition to the primary end point of evaluating the overall completeness of reporting of RCTs, 1) we attempted to detect if there was an improvement of compliance over time. To test for reporting differences over time, studies were grouped by year starting from 2011 and reaching to 2016 (six groups: 2011-2012-2013-2014-2016). 2) We also separated the checklists' items into four groups according to the sections of the published article: i) Title/Abstract & Introduction, ii) Methods, iii) Results, vi) Discussion & Other information and then we calculated the compliance of the checklist items in each of the 4 groups. 3) We collected information on the number of patients that were randomized in each trial and examined possible association with reporting. 4) Finally we examined if the impact factor of the journal where the trial was published was associated with the number of reported items. 5) A subgroup analysis of completeness of reporting for the five key methodological factors described earlier was also carried over.

Statistical Analysis

We calculated the various frequencies of compliance as a percentage after adjusting for checklist items which were not applicable in certain RCTs. So the general formula we used for **compliance** is:

$$\textbf{Compliance}\ (\%) = \frac{\boldsymbol{Reported\ items(YES)}}{\boldsymbol{Applicable\ Items}} \textbf{*100\%}$$

Were, ***applicable items = total items - non applicable items***

Were, ***total items = Reported (YES + NO) + non_applicable items.***

So, ***applicable items = Reported (YES + NO)***

So for example the frequency of compliance for the 1st RCT is:

$$\text{Freq(1stRCT)\%} = \frac{\boldsymbol{YES}\ \text{in the 1st RCT}}{\text{total} - \text{non applicable items}} \textbf{*100= } \frac{\textbf{26}}{\textbf{37}-\textbf{3}} \textbf{*100= 76,4\%}$$

1) We calculated the overall number of checklists items reported and estimated overall compliance (as a proportion). 2) The number and proportion of checklist items reported in each trial, as well as the number and proportion of checklist items reported in each trial by time period was calculated. We then calculated the number and proportion of articles, overall and by time period, which had addressed at least the 75% of the checklists' items (i.e. articles' (>75%) compliance). The 75% cut-off point of compliance has been used previously as an adequate measure of compliance in various studies [32, 45]. We used the Pearsons' chi-squared statistic to compare the 75% compliance of trials between the 6 time periods. 3) Moreover the number and proportion of each CONSORT items being reported by articles was estimated for the whole time period (i.e. how many times each checklist item was reported as an absolute number and proportion). Also the proportion of checklists items being reported by year was reported. We then calculated the number and proportion of checklist items, which were reported in at least 75% of the trials (i.e. checklist (>75%) compliance), overall and by year. We used Pearsons' chi-squared statistic to examine whether the (>75%) compliance of reported items improved over time. 4) We calculated the number and proportion of trials reporting each checklist item by group (i.e. how many times are checklist items reported in their group. 4 groups i) Title & Abstract, ii) Introduction, iii) Methods, iv) Results, v) Discussion & Other information}. We then calculated the number and proportion of "checklists' 75% compliance" in each group (i.e how many items with (>75%)compliance in the articles are found in each group). 5) Pearson's correlation analysis was performed to examine the relationship of completeness of reporting i) with the number of the participants randomized in each trial & ii) with the impact factor of the journal. 6) We calculated the number and proportion of the "5 key methodological factors" reported in each trial and then estimated the compliance overall and by time period. We compared compliance between two time periods (May 2001-2013) & (2014- May 2016) using Hotteling's T-test. The impact factor of the journals was retrieved from the Thomson Reuters Citation Reports web site. Evaluation of the CONSORT items in the 55 RCTs and calculation of the corresponding frequencies was done with the use of Microsoft Excel 2007. All statistical analyses were made on the IBM SPSS v.22 package. The cutoff point for statistical significance was set at the two-sided 0.05 level. Data extraction and article assessment was made by one author (NP).

RESULTS

The screening process for acquiring the eligible RCTs was executed in four steps. The first search meeting of the electronic database "Pubmed" was established on 1st May 2016 and it procured 539 related articles according to the search criteria mentioned above. From the 539 articles 103 were excluded as irrelevant by screening the title alone (observational/ non-interventional studies, non-theurapeutic intervention, non-randomized trials, post-hoc/ sub-group analysis or trials not relevant with multiple myeloma). The remaining 436 articles were reviewed by abstract and thus excluding 299 more non-eligible articles. Finally the last 137 articles after being reviewed by full text 82 were found irrelevant, leaving 55 eligible articles to be included in the study. A list of the 55 RCTs that included a total of 21.761 patients, as well as the flowchart (figure_1) of the screening process can be retrieved in the Supplementary material (APPENDIX).

Overall compliance, compliance per article, (>75%)compliance per article & by time period

Out of the total 55 eligible articles, 7 were published in 2016 (May), 11 in 2015, 6 in 2014, 11 in 2013, 14 in 2012 and 6 in 2011(May), all in the last 5 years (May 2011 – May 2016)from the time we began our search. The articles were published in 18 different medical journals with mean Impact Factor: "20.2", min: "2.06" and max: "55.87". **The overall CONSORT compliance score was 63,10%**.

Table 1

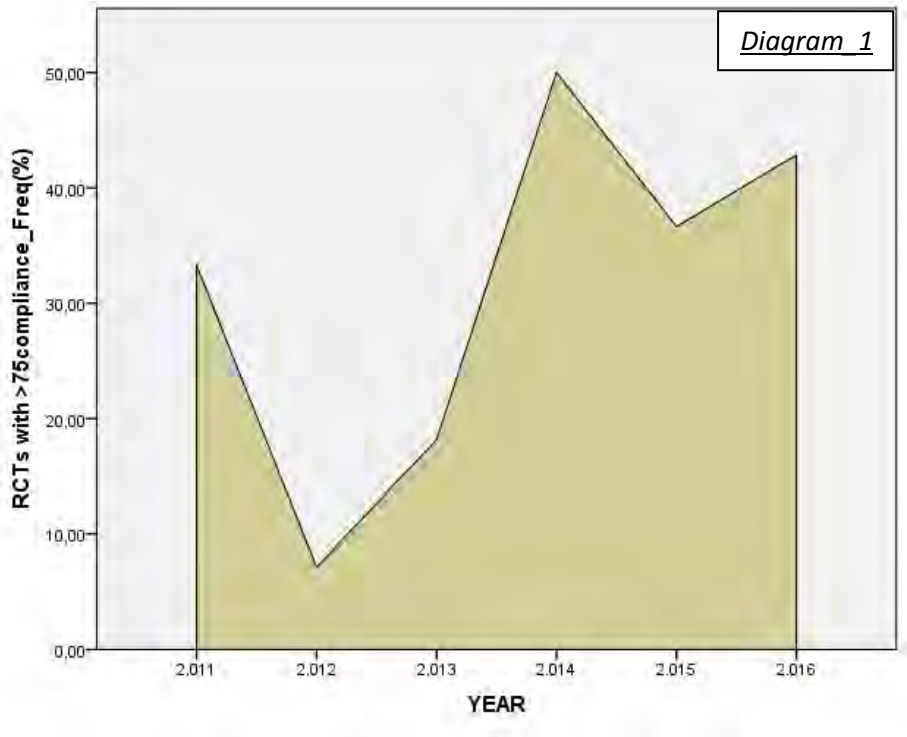
Year		Journal	
2016(May)	7	Blood	14
2015	11	N Engl. J Med.	9
2014	6	Lancet Oncol.	7
2013	11	J Clin Oncol	4
2012	14	Haematologica	3
2011(May)	6	Others	18
Total	55	Total	55

The RCTs that covered more than 75% of the CONSORT items were **15 (27.20%).** The average compliance by time period as well as the absolute number and proportion of RCTs with (>75%) compliance by time period are presented on the table bellow (table 2).

Table 2

Year	Total RCTs per year	Number of RCTs with >75% compliance	Proportion of RCTs with >75% compliance (%)	Compliance per year (%)
2016	7	3	42,85	67,67
2015	11	4	36,65	67,90
2014	6	3	50	71,43
2013	11	2	18,18	61,71
2012	14	1	7,14	57,93
2011	6	2	33,3	54,97
Total	**55**	**15**	**27,2**	**63,10**

As we can observe from the diagram bellow (*diagram 1*), there seems to be a tendency towards better 75% compliance of the articles over time, (i.e. there seems to be more articles with >75% compliance over time) . We tested this hypothesis using a chi-squared test for a two by six (2*6) table. However, even if the percentages of RCTs that have 75% compliance seems to grow over time, this difference is non-significant for a possibility of error of 5%, since p = 0,27 > 0,05. (More information on the 2x6 table and the Pearson Chi-Square test can be found in the APPENDIX).



Absolute numbers and proportional compliance of items reported in each trial, along with: numbers of non-applicable CONSORT items in each trial, the number of patients that were randomized in each trial and the Journal where each trial was published, with the corresponding Impact Factor are presented on *table 3* bellow.

Table 3

No. RCTs	Year	Items Reported	non-applicable items	Compliance (%)	JOURNAL	Impact Factor	Randomized Participants
1	2016	26	3	76,47	N Engl J Med.	55.873	722
2	2016	17	6	54,84	Blood	10.452	668
3	2016	26	4	78,79	Lancet	45.217	124
4	2016	21	2	60,00	Blood	10.452	662
5	2016	29	3	85,29	Lancet Oncol	24.69	929
6	2016	19	3	55,88	Ann Hematol	2.634	82
7	2016	19	6	61,29	Blood	10.452	233
	Total	131	27	67,67			3.420
8	2015	30	4	90,91	Lancet Oncol	24.69	256
9	2015	19	3	55,88	Blood	10.452	306
10	2015	17	8	58,62	Haematologica	-	100
11	2015	26	4	78,79	J Clin Oncol	18.428	502
12	2015	24	5	75,00	N Engl J Med.	55.873	646
13	2015	22	4	66,67	Br J Haematol	4.711	95
14	2015	12	3	35,29	Blood	10.452	40
15	2015	23	4	69,70	Biomed Res Int	-	209
16	2015	23	13	95,83	BMJ Open	2.063	
17	2015	21	5	65,63	N Engl J Med.	55.873	792
18	2015	22	2	62,86	Am J Hematol	3.798	281
	Total	239	55	67,90			3.227
19	2014	28	1	77,78	Lancet Oncol	24.69	768
20	2014	23	5	71,88	N Engl J Med.	55.873	524
21	2014	26	5	81,25	N Engl J Med.	55.873	1623
22	2014	30	4	90,91	Lancet Oncol	24.69	174
23	2014	13	6	41,94	Blood	10.452	106
24	2014	20	5	62,50	Blood	10.452	221

	Total	140	26	71,43			3.416
25	2013	24	5	77,42	Lancet Oncol	24.69	637
26	2013	29	4	87,88	Lancet Oncol	24.69	455
27	2013	18	4	54,55	N Engl J Med.	55.873	125
28	2013	18	5	56,25	Biol Blood Mar	3.404	50
29	2013	16	4	48,48	Blood	10.452	370
30	2013	22	5	68,75	Blood	10.452	455
31	2013	21	5	65,63	Blood	10.452	332
32	2013	18	8	62,07	J Clin Oncol	18.428	98
34	2013	9	5	28,13	Cancer Immunol	3.941	48
35	2013	21	5	65,63	Leukemia	10.431	68
36	2013	20	6	64,52	Cancer	-	102
	Total	216	56	61,71			2.740
33	2012	11	14	47,83	BMC Cancer	3.362	302
37	2012	22	4	66,67	J Clin Oncol	18.428	827
38	2012	16	6	51,61	Blood	10.452	390
39	2012	21	4	63,64	Am J Hematol	3.798	1213
40	2012	21	4	63,64	J Clin Oncol	18.428	269
41	2012	18	0	48,65	N Engl J Med.	55.873	460
42	2012	22	2	62,86	N Engl J Med.	55.873	459
43	2012	23	0	62,16	N Engl J Med.	55.873	614
44	2012	21	3	61,76	Blood	10.452	158
45	2012	24	5	75,00	Eur J Haematol.	2.066	131
46	2012	16	6	51,61	Haematologica	-	499
47	2012	17	5	53,13	Haematologica	-	1114
48	2012	18	5	56,25	Eur J Haematol.	2.066	400
50	2012	13	6	41,94	Cancer	-	60
	Total	263	64	57,93			6.896
49	2011	10	6	32,26	Immunotherapy	2.44	682
51	2011	19	6	61,29	Blood	10.452	199
52	2011	14	4	42,42	Ann Hematol	2.634	91
53	2011	26	6	83,87	Blood	10.452	856
54	2011	9	3	26,47	Br J Haematol	4.711	12
55	2011	27	6	87,10	Lancet Oncol	24.69	222
	Total	105	31	54,97			2.062
Sum		**1022**	**259**	**63,10**		Mean:20.2	21.761

Compliance per item & (>75%) compliance of items by time period

The absolute numbers and proportions of items being reported by the articles overall as well as the proportions per year by year can be found on table 5.

Table 5

	Reported Items	**Compliance (%)**	**2016**	**2015**	**2014**	**2013**	**2012**	**2011**
Abstract/title								
1a	30	54,5	28,57	54,55	66,67	63,64	64,29	33,33
1b	11	20	28,57	18,18	66,67	18,18	0	16,67
Introduction							64,29	
2a	**49**	**89,1**	**100**	**100**	**100**	**90,91**	**100**	**100**
2b	**52**	**94,5**	**85,71**	**100**	**83,33**	**45,45**	**35,71**	**100**
Methods								

3a	27	49,3	57,14	45,45	83,33	100	40	50
3b	11	73,3	100	100	0	72,73	92,86	40
4a	**46**	**83,6**	**85,71**	**90,91**	**100**	**45,45**	**35,71**	50
4b	29	52,7	57,14	54,55	83,33	90,91	100	66,67
5	**52**	**94,5**	**100**	**100**	83,33	**72,73**	**85,71**	83,33
6a	**45**	**81,8**	**85,71**	**90,91**	**100**		**50**	**50**
6b	1	33,3			0	81,82	71,43	
7a	**42**	**76,4**	**85,71**	**72,73**	**100**	**100**	**50**	50
7b	19	63,3	80	62,50	33,33	18,18	21,43	
8a	17	30,9	42,86	45,45	33,33	54,55	50	33,33
8b	30	54,5	71,43	63,64	50	18,18	14,29	33,33
9	16	29.1	42,86	27,27	66,67	18,18	0	33,33
10	10	18,2	28,57	27,27	16,67	20	16,67	33,33
11a	7	30,4	0	42,86	100	20	0	50
11b	5	22,7	0	33,33	100	81,82	92,86	50
12a	**46**	**83,6**	**85,71**	**81,82**	100	**71,43**	**84,62**	50
12b	**37**	**78,7**	**57,14**	**100**	100	**81,82**	**84,62**	50
Results								
13a	**44**	**83**	85,71	**90**	**66,67**	**71,73**	**61,54**	83,33
13b	37	69,8	71,43	70	83,33	90,91	85,71	66,67
14a	41	74,5	28,57	90,91	83,33	100	100	33,33
14b	**11**	**91,7**	**100**		**50**	**100**	**100**	100
15	**52**	**98,1**	**100**	**100**	**100**	**63,64**	**69,23**	83,33
16	34	64,2	57,14	70	50	81,82	92,31	**66,67**
17a	44	83	85,71	80	66,67	45,45	38,46	**83,33**
17b	**31**	**58,5**	**85,71**	**80**	**50**	**40**	**83,33**	66,67
18	32	74,4	85,71	62,65	80	81,82	84,62	**83,33**
19	**48**	**90,6**	**100**	**90**	**100**	**54,55**	**14,29**	100
Discussion								
20	21	38,2	57,14	45,45	50	54,55	28,57	**16,67**
21	29	52,7	57,14	72,73	83,33	100	100	**33,33**
22	**53**	**98,1**	**100**	**100**	**100**	**45,45**	**14,29**	83,33
Other Information								
23	18	32,7	57,14	27,27	33,33	9,09	21,43	**33,33**
25	9	16,4	14,29	18,18	33,33	54,55	57,14	0
25	34	61,8	71,43	81,82	66,67			**33,33**
Total	**1120**	**63,10**						

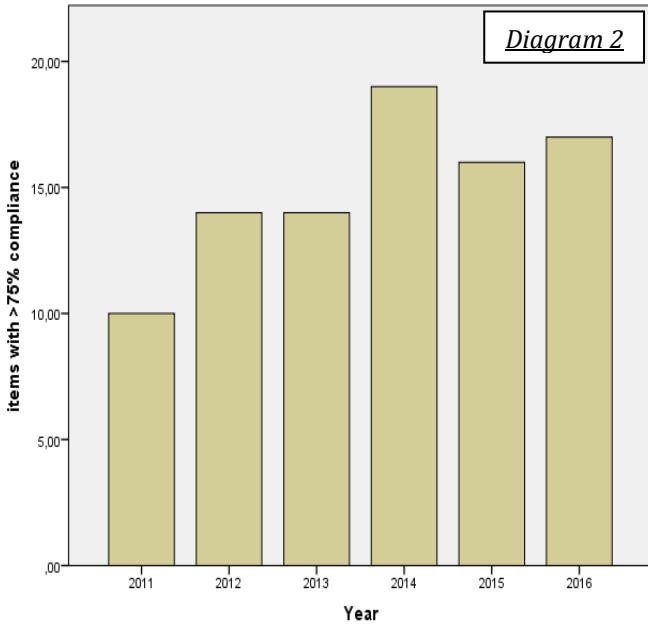
The whole time period (May 2011- May 2016) 14 items (62,2%) were reported in more than 75% of the 55 articles {checklists' (>75%) compliance}. These checklist items were: **2a, 2b, 4a, 5, 6a, 7a, 12a, 12b, 13a, 14b, 15, 17b, 19 and 22.**

The number and percentages of CONSORT items reported by more than 75% of the articles by time period are presented in *table 6*, while *diagram 2* shows the number of CONSORT items with (>75%) compliance over time.

Table 6

Year	Number of items with >75% compliance	Proportion of items with >75% compliance (%)
2016	17	47,22
2015	16	45,71
2014	19	51,35
2013	14	38,89
2012	14	37,84
2011	10	29,41

Diagram 2



Although the number of CONSORT items which are reported in articles each year seem to increase slightly (i.e. more and more items seem to achieve (>75%) reporting from articles every year), the difference in the increase is not statistical significant (p= 0,49 > 0,05). More detailed information about the Pearson chi-squared test of the 2x6 table can be found in the appendix)

Number and proportion of trials reporting each checklist item by group

As we mentioned before a total of 14 CONSORT items were reported in the 55 articles. The numbers and proportions of items with (>75%) compliance group, as well as the average compliance per group are presented on the *table 7* bellow.

Table 7

Group	Number of items with (>75%) compliance	Percentage of items with (>75%) compliance (%)	Compliance per group (%)
Title/abstract & Introduction	2	50	64,5
Methods	6	35,3	56,3
Results	5	50	78,8
Discussion & Other Information	1	16,7	50

Association with Impact Factor & Number of Randomized participants

i) As far the association of completeness of reporting with the Impact Factor of the journal where the article was published is concerned, we found out that the impact factor does correlate positively with the reporting of checklists' items. More specifically we found a positive **R= 0.308** with possibility for error less than 5**%, (p=0,032< 0, 5)**. However **R-squared= 0,095**, which means that only 9, 5% of the variation of the reporting can be accounted for by the Impact Factor. Even so, we have proven that journals with higher Impact Factor, affect positively reporting.

ii) Moreover we revealed a positive association between the number of the randomized participants and the completeness of reporting. In this case we found a positive **R= 0,320** with a possibility for error less than 5% (**p=0,018**) and **R-squared=0,102**.

As a next step we tried to identify how well is the "frequency of reporting" described by the "Impact Factor" together with the "number of the randomized participants". To examine this correlation we created a linear regression line which included these two variables. However we found out that when

we enter these two variables in the regression equation together, their coefficients cannot account for the reporting frequency in a statistical important standard.

-> "reporting quality"= 0,012*Randomized_participants + 0,223*Impact_Factor, were p=0,08 & p=0,07 for the Randomized_participants & the Impact_Factor accordingly.

We noticed next that when we examine the correlation of the Impact Factor with the reporting quality, adjusted for the number of participants, as well as the correlation of the number of participants with the reporting quality, adjusted for the Impact Factor, these associations ceased to be statistically important.

(Additional information about the Pearson's bivariate correlation, the partial correlation and the regression line we employed can be found in the Appendix).

Compliance of "5 key methodological factors"

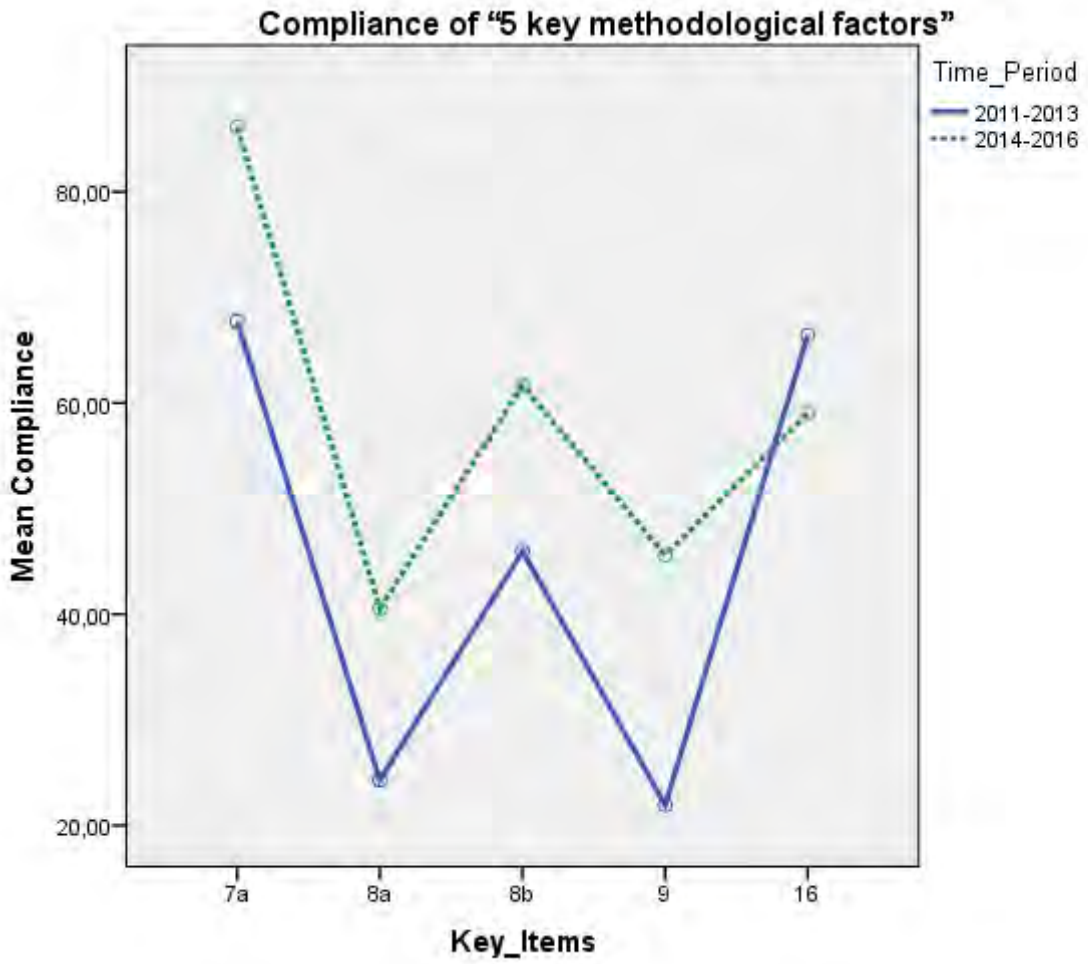
The overall compliance of the "5 key methodological factors" is **50,91%,** while only 7 out of the 55 articles (12,7%) report completely these factors. On the table below the proportion of reporting of each factor by year, as well as the average compliance per year is presented.

Table 8

(%)	2016	2015	2014	2013	2012	2011	Total
7a	85,71	72,73	100,00	81,82	71,43	50,00	76,4
8a	42,86	45,45	33,33	18,18	21,43	33,33	30,9
8b	71,43	63,64	50,00	54,55	50,00	33,33	54,5
9	42,86	27,27	66,67	18,18	14,29	33,33	29,1
16	57,14	70,00	50,00	63,64	69,23	66,67	64,2
Total	**60**	**55,56**	**60**	**47,27**	**44,43**	**43,43**	**50,91**

We wondered whether the reporting of these "5 key methodological factors" differed over time. For this reason we compared two time periods: (2011-2013) & (2014-2016). In order to examine if the two time periods differed based on the reporting of these 5 factors combined, we will use Multivariate Analysis of Variance (MANOVA).

From the diagram bellow we notice that the (2014-2016) time period seems to have a better reporting quality from the time period (2011-2013), with the 2 lines being in most cases substantially far from each other. Moreover we get a mean for time-period (2016-2014) =58, 6%, and a mean for time-period (2013-2011)= 45,3%. From the "Multivariate analysis" the Hotteling's test shows us that a statistical significant difference exists for the time period, where **p= 0,038 < 0,05**, which means that **the time periods differ with a possibility of error less than 5%** . (Additional details for the above analysis can be found in the APPENDIX)



DISCUSION

The randomized controlled trial, more than any other methodology, can have a powerful and immediate impact on patient care. Ideally, the report of such an evaluation needs to convey to the reader relevant information concerning the design, conduct, analysis, internal validity and generalizability of the trial. For RCTs to ultimately benefit patients, the published report should be of the highest possible standard [21], since as Schulz et al concluded in his study [20], without adequate reporting, assessing quality becomes impossible.

Analysis

However evidence has accumulated to suggest that the reporting of RCTs remains sub-optimal [35]. The results of the present study show a similar trend, with essential aspects of RCTs involving patients with multiple myeloma being seldom described. **Overall compliance** with the Consort Statement is unsatisfactory displaying a proportion of **63.10%** adequate reporting, while for the time period May 2011- May 2016 only **15 out of 55 articles**, which is less than one-third (**27,3%**), reported at least 75% of the CONSORT items. At the same time only **14 out of 37 (37,8%)** CONSORT items were addressed in 75% or more of the studies published the last five years (May 2011 - May 2016). Some CONSORT items were generally underreported. The least reported item was **24** "where the full trial protocol can be accessed, if available", which is a recent addition to the revised 2010 CONSORT checklist. A more important finding is that significant methodological information was also underreported such as **item 8a** "method used to generate the random allocation sequence" and **item 9** "mechanism to implement the random allocation sequence describing any steps taken to conceal

the sequence until interventions were assigned" which were reported only in **30,9%** and **29,1%** respectively. These inadequacies are not to be taken lightly. Mosteller et al described randomization as a principal bias-reducing technique used in clinical trials and continued saying that the method used and how well it was followed help determine the credence the reader will have in the reported conclusions of a study. He also commented that "When the randomization leaks, the trial's guarantee of lack of bias runs down the drain", thereby published reports of clinical trials should briefly describe how the randomization was actually done. Only then can the reader properly evaluate the trial [22]. Moreover a number of CONSORT items being non-applicable for some of the RCTs were found, especially item 6b "any changes to trial outcomes after the trial commenced, with reasons" was not applicable in 94,5% of the articles. Concerning the group distinction according to the sections of the article, the part of the "results" tended to be better reported with an average compliance of 78,8%, while the least reported section was the "discussion & other information" with 50% compliance.

We couldn't prove that a significant improvement in the reporting quality of the articles over time existed. Moreover there was no significant increase to be found in the number of the CONSORT items that were reported each year. Although in both cases a trend towards better compliance seemed to appear. These findings are similar to that of Djulbegovic et al, who reported that the quality of RCT reports in multiple myeloma is modest at best, "clouding the scientific interpretation and immediate clinical usefulness of these studies"[4]. Another study assessing CONSORT compliance in myeloid malignancies (acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and myelodysplastic syndromes (MDS) [32] found a statistical significant improvement over time only in some reporting items, while several other important methodological descriptions improved only minimally, which comes in terms with the findings of our study, especially when considering the results of our subgroup analysis which showed promising reporting over time in the sub-group items examined. A more recent study judging the completeness of reporting in RCTs involving patients with multiple sclerosis reported more promising results. Although Rikos et al [45] stated that the overall quality of reporting in their study was not optimal presenting a low overall compliance rate of 68.2%, quite similar to ours (63,10%), they managed to prove that an improvement over time existed, with a statistical significant increase ($p< 0,05$) in the reporting of more than 75% of CONSORT items during the three five-year periods (from 2000 to 2015) that they compared. In our sub-group analysis of the "5 key methodological factors" we found that the two *time periods (2011-2013 & 2014-2046) differed in the reporting of these 5 factors overall* ***(p<0,05)***, with the time period 2013-2016 showing better compliance. Apart from that we found a positive *association between the Impact Factor* where the RCT was published *and the reporting compliance*. A way to interpret this finding is that RCTs published in high impact factor journals have a better reporting quality, perhaps because of the policies implemented in these journals. However we examined two more correlations which could change our view over the subject. We proved that the *number of randomized participants* was associated not only with the *reporting quality*, but also with the *Impact Factor* itself. In other words bigger and as such more significant studies were better reported **(r=0,320 & p=0,018<0,05)** and because of their significance they tended to be published in more prominent journals **(r=0,375 & p=0,009<0,05)**, as these journals are characterized by their Impact Factor. This explains the fact that when we examined the correlation of the reporting frequency with the Impact Factor, adjusted for the size of the study (i.e. the number of randomized participants) the association ceased to be statistically important **(p= 0,07 >0,05)**

Limitations

A limitation to our study is that the time period from May 2011 to May 2016 that we used to analyze the reporting quality of RCTs is rather small, and may not be enough to identify significant differences in reporting quality through time. Also by choosing as a time period the last 5 years from the time we first began our search (May 2011- May 2016) we couldn't as a result include all the trials published in 2011 (and of course 2016), and therefore bias could be introduced in our year by year comparisons. Moreover, taking into account that the evaluations of the CONSORT items are in a large part subjective, another potential limitation to our study is that all the data were extracted and analyzed by one reviewer, so there was no way to compensate for any bias that might have occurred

from misjudged evaluations. Apart from that, the fact that we included in our study articles published only in English could introduce bias, however the number of articles that we retrieved using the PubMed search engine written in another language was not significant (18 out of 557 or 2,3%). In relation to the sub-group analysis, major concerns have been raised whether choosing 5 out of the 37 CONSORT items to analyze separately would introduce bias. However the selection of these factors had been predetermined prior to any statistical analysis, and also their choice was not arbitrary. We decided to include these factors in our separate analysis, after reviewing several other studies [4, 20, 26, 40, 48, 49], which addressed the problem of reporting of RCTs especially, those before 1996 prior to the announcement of the CONSORT statement. We concluded to these 5 items after identifying the most common factors reported by these studies. Finally we feel that our results could be cautiously generalized beyond the Hematology field and the Multiple Myeloma disorder in particular, although evaluations about reporting quality in other medical conditions have reached similar conclusions to ours.

Conclusion

CONSORT, came about because of the need to provide readers with enough valid and meaningful information concerning the design, conduct, and analysis of RCTs, therefore it is expected that the CONSORT statement will ultimately lead to more comprehensive and complete reporting of RCTs [21]. However our results summarized indicate that reports of RCTs involving patients with Multiple Myeloma do not as yet conform to the CONSORT recommendations, neither have we found strong indications of improvement over time.

Although in proposing structured reporting the main objective was not to pass judgment on the quality of the trial itself, but to improve on how it is reported to the reader [18], it is generally accepted that the methodological quality of a trial is closely intertwined with the quality of reporting [33]. {*Note that the CONSORT 2010 Statement does not include recommendations for designing, conducting, and analyzing trials. It solely addresses the reporting of what was done and what was found [29]*}. A principal advantage of such reporting is that all readers will have uniform and standardized information to review, unaffected by the writing nuances of authors and the policies of editors. This will give readers essential information about what happened during the trial, especially around issues affecting a trial's internal validity [18]

The significance of knowing the status quality of the reporting of RCTs can be easily appreciated when we consider the simple fact that physicians, health policy makers and patients have to base their decisions on the available published information [4]. Taking into account all of the above, the results of our review can only suggest that further actions should be taken by authors, reviewers, and editors, since inadequate reporting makes the interpretation of RCTs difficult if not impossible.

To conclude I replicate [16] the words of a passage that Hill [15] quoted from an editorial in British Medical Journal, which can clearly describe the significance of the issue under discussion:

> *"In treating patients with improved remedies we are, whether we like it or not, experimenting on human beings, and a good experiment* ***well reported*** *may be more ethical and entail less shirking of duty than a poor one".*

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APPENDIX

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<u>Flow-chart of screening strategy</u>

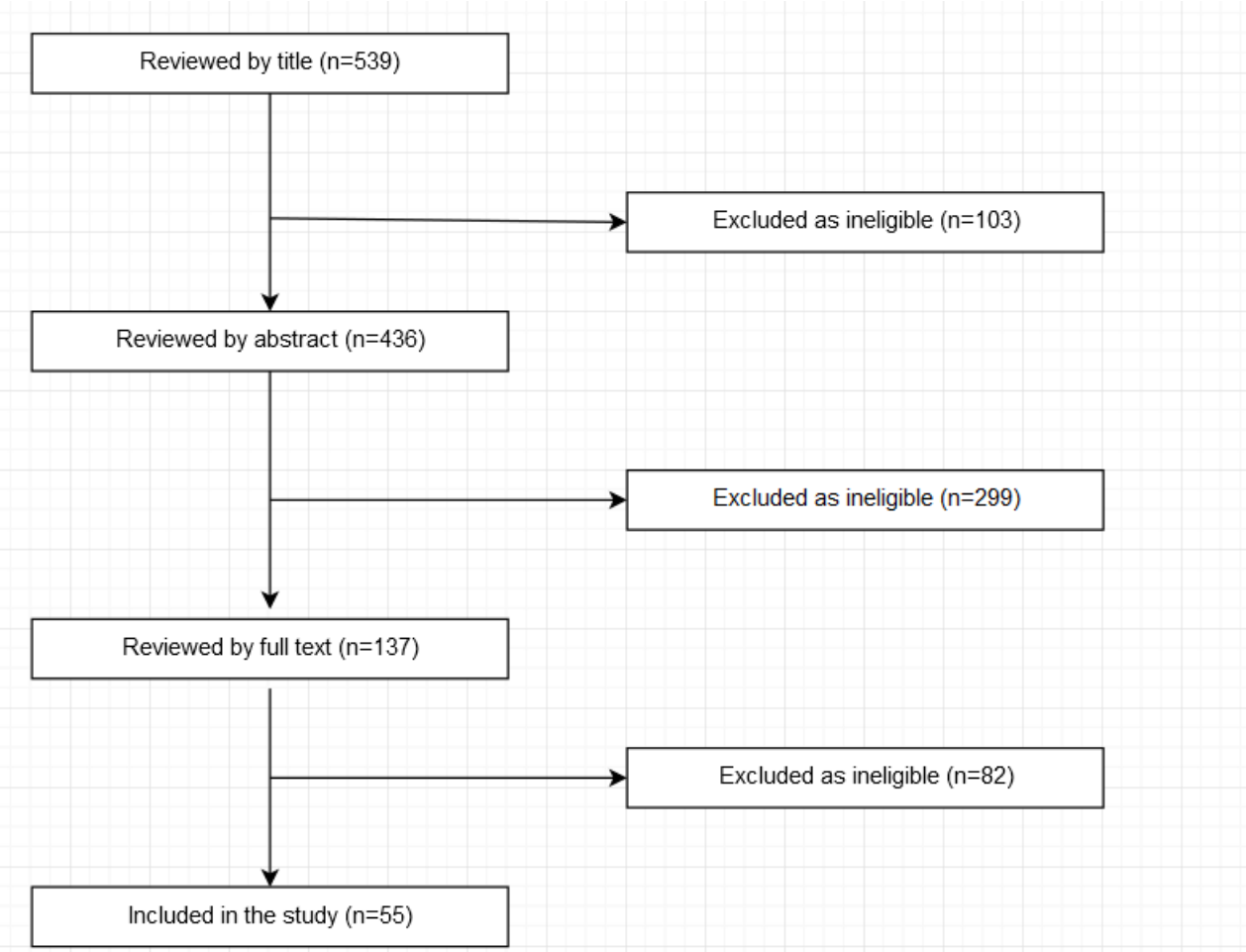

Fig.1 Flow chart of search strategy

- ***2x6 table and the Pearson Chi-Square test comparing the (>75%) compliance of RCTs, over time.***

TIME * COMPLIANCE_75 Crosstabulation

Count

		COMPLIANCE_75		
		(-) 75%COMPLIANC	(+) 75%COMPLIANCE	Total
TIME	2016	4	3	7
	2015	7	4	11
	2014	3	3	6
	2013	9	2	11
	2012	13	1	14
	2011	4	2	6
Total		40	15	55

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6,308[a]	5	,277
Likelihood Ratio	6,882	5	,230
Linear-by-Linear Association	2,667	1	,102
N of Valid Cases	55		

a. 8 cells (66,7%) have expected count less than 5. The minimum expected count is 1,64.

The associations of the completeness of reporting i) with the number of the participants randomized in each trial & ii) with the impact factor of the journal
As far the association of completeness of reporting with the impact factor of the journal where the article was published is concerned, we found out that the impact factor does correlate positively with the reporting of checklists' items. More specifically we found a positive R= 0.308 with possibility for error less than 5%, (p=0,032< 0, 5). However R-squared= 0,095, which mean that only 9, 5% of the variation of the reporting can be accounted for by the Impact Factor. Even so, we have proven that journals with higher Impact Factor, affect positively reporting.

- ***<u>The associations of the completeness of reporting i) with the number of the participants randomized in each trial & ii) with the impact factor of the journal</u>***
    - Pearson's correlation for:
        - Compliance & Randomized Participants
        - Compliance & Impact Factor
        - Randomized Participants & Impact Factor
    - Linear Regression lines for Randomized Participants, Impact Factor, Randomized Participants & Impact Factor
    - Adjusted correlations

Correlations

		Compliance	Randomized_participants	Impact_Factor
Compliance	Pearson Correlation	1	,320*	,308*
	Sig. (2-tailed)		,018	,032
	N	55	54	49
Randomized_participants	Pearson Correlation	,320*	1	,375**
	Sig. (2-tailed)	,018		,009
	N	54	54	48

Impact_Factor	Pearson Correlation	,308*	,375**	1
	Sig. (2-tailed)	,032	,009	
	N	49	48	49

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Impact Factor

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1217,343	1	1217,343	4,912	,032[b]
	Residual	11649,174	47	247,855		
	Total	12866,517	48			

a. Dependent Variable: Compliance

b. Predictors: (Constant), Impact_Factor

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,308[a]	,095	,075	15,74340

a. Predictors: (Constant), Impact_Factor

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	58,602	3,301		17,750	,000	51,960	65,244
	Impact_Factor	,264	,119	,308	2,216	,032	,024	,504

a. Dependent Variable: Compliance

Randomized Participants

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1282,783	1	1282,783	5,915	,018[b]
	Residual	11276,979	52	216,865		

	Total	12559,762	53			

a. Dependent Variable: Compliance

b. Predictors: (Constant), Randomized_participants

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,320[a]	,102	,085	14,72634

a. Predictors: (Constant), Randomized_participants

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	56,723	3,123		18,161	,000	50,455	62,990
	Randomized_participants	,014	,006	,320	2,432	,018	,003	,026

a. Dependent Variable: Compliance

Adjusted correlations for 1) Randomized Participants, 2) Impact Factor

Correlations

Control Variables			Compliance	Impact_Factor
Randomized_participants	Compliance	Correlation	1,000	,267
		Significance (2-tailed)	.	,070
		df	0	45
	Impact_Factor	Correlation	,267	1,000
		Significance (2-tailed)	,070	.
		df	45	0

Correlations

Control Variables			Compliance	Randomized_participants
Impact_Factor	Compliance	Correlation	1,000	,258
		Significance (2-tailed)	.	,080
		df	0	45
	Randomized_participant	Correlation	,258	1,000

	s	Significance (2-tailed)	,080	.
		df	45	0

Randomized Participants & Impact Factor

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2264,535	2	1132,268	5,327	,008[b]
	Residual	9565,005	45	212,556		
	Total	11829,540	47			

a. Dependent Variable: Compliance

b. Predictors: (Constant), Impact_Factor, Randomized_participants

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	53,654	3,639		14,744	,000	46,324	60,983
	Randomized_participants	,012	,007	,259	1,793	,080	-,002	,026
	Impact_Factor	,223	,120	,268	1,857	,070	-,019	,466

a. Dependent Variable: Compliance

Comparison of the CONSORT items reported with (>75%) compliance each year

Year * (>75%)compliance Crosstabulation

Count

		(>75%)compliance		
		NO	YES	Total
Year	2011	45	10	55
	2012	41	14	55
	2013	41	14	55
	2014	36	19	55
	2015	39	16	55
	2016	38	17	55

Total	240	90	330

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4,400[a]	5	,493
Likelihood Ratio	4,522	5	,477
Linear-by-Linear Association	2,763	1	,096
N of Valid Cases	330		

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 15,00.

Comparison of the Compliance of "5 key methodological factors" between two time periods (May 2001-2013) & (2014-May 2016)

MANOVA-Hotelling's test

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	1,000	14722,830[b]	4,000	1,000	,006	1,000
	Wilks' Lambda	,000	14722,830[b]	4,000	1,000	,006	1,000
	Hotelling's Trace	58891,322	14722,830[b]	4,000	1,000	,006	1,000
	Roy's Largest Root	58891,322	14722,830[b]	4,000	1,000	,006	1,000
Time_Period	Pillai's Trace	,999	387,095[b]	4,000	1,000	,038	,999
	Wilks' Lambda	,001	387,095[b]	4,000	1,000	,038	,999
	Hotelling's Trace	1548,381	387,095[b]	4,000	1,000	**,038**	,999
	Roy's Largest Root	1548,381	387,095[b]	4,000	1,000	,038	,999

a. Design: Intercept + Time_Period

b. Exact statistic