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Original Article

A study comparing trial registry entries of randomized controlled trials with publications of their results in a high impact factor journal: The Journal of the American Medical Association

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Abstract

Purpose: The International Committee of Medical Journal Editors mandates trial registration as a precondition for publication. Growing evidence indicates that information in registry may not correlate with eventual publication. The present study was carried out with the objective of comparing content of Randomized Controlled Trials (RCTs) published in one year in the Journal of the American Medical Association (JAMA), with the information contained in trial registries.

Methods: All RCTs published in JAMA in 2013 were included. 11 data set items were matched for content between registry entry and published RCT: Title, Primary and Secondary Objectives, Study type, Inclusion and Exclusion Criteria, Treatment Age Group, Follow up, Sample Size, Primary and Secondary Outcomes. A fully correct match was scored 2, partially correct 1 and incorrect 0. Thus, maximum possible score for each paper was number of items multiplied by 2, i.e., 22.

Results: The median [range] total score achieved by RCTs was 15. No RCT achieved a perfect score of 22. The largest proportion of RCTs reported secondary objectives, study type, treatment age group, follow up, sample size and primary outcomes fully correctly. However, only 13.5 %, 12 % and 13.5 % of RCTs were a perfect match with registry entries in terms of title, primary objective and secondary outcomes respectively. Almost three quarters did not match perfectly in selection criteria.

Conclusion: There exist discrepancies between trial registration and published paper even in a high impact factor journal. Both authors and editors should adhere to CONSORT guidelines to ensure transparency of published research.

Keywords: Data set items, discrepancy, registry, scoring system

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INTRODUCTION

In response to the Food and Drug Administration Modernization Act of 1997, the National Institutes of Health launched the ClinicalTrials.gov website in 2000.[1] In the same year, the Declaration of Helsinki stated for the first time that "The

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design of all studies should be publicly available" and further that "Negative as well as positive results should be published or otherwise publicly available."[2] The 2008 version of the same guideline required that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."[3] The WHO launched the International Clinical Trials Registry Platform in 2007, which provided a single point of access to studies registered in various international registries.[4]

In 2005, the International Committee of Medical Journal Editors (ICMJE) issued a requirement for a trial to be registered as a precondition for a publication.[5] The CONSORT statement (2010) similarly required the final publication to carry the trial registration number.[6] However, in practice, registration may be not be done, may be postdated,[7] or information provided in the trial registry may not correlate with the eventual publication.[8]

The Journal of the American Medical Association (JAMA) is a widely read, multispecialty journal and publishes the results of several randomized controlled trials (RCTs) which contribute to a high level of evidence that impacts clinical practice worldwide. We thus carried out the present study with the objective of comparing the content of RCTs published in 1 year in this journal, with the information contained in the trial registries where the studies were registered.

MATERIALS AND METHODS

Ethics

The study was granted exemption from review by the Institutional Ethics Committee (EC/OA–54/2015).

Selection criteria

All RCTs published in JAMA in the year 2013 were included in the analysis while review articles, observational studies, meta-analyses, and extension studies of RCTs were excluded from the analysis.

Study procedure

Every RCT published was searched for the trial registration number, which was then used to track the registry entry. If no registration number was reported, the corresponding author was contacted by E-mail for this information. If we received no answer from the corresponding author, we searched the following clinical trial registries: ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register, and the registry of the country of the first or corresponding author. If no registration number was found at the end of this process, the published study was considered not registered and excluded from the analysis.

Data extraction

Data were extracted from the registry entries and the published RCTs by four authors - PW , PG, AP, and SC and verified by ML. Data were cross-checked by NG and UT. Any dispute was resolved by discussion. A total of 11 data set items were noted from the registry record: study title (both the working title and scientific title), primary and secondary objectives, study type (e.g., whether placebo controlled or not, whether blinded or not, phase of drug development, single center or multicenter), inclusion and exclusion criteria, treatment age group, time points for follow-up, sample size, and primary and secondary outcome measures. Each item extracted from the registry was matched for content with the corresponding item in the published RCT.

In addition, we also classified the health condition studied by the RCT into a broad therapeutic area and confirmed in each published RCT whether any change made in the trial was stated with reasons.

Scoring system used and statistics

We developed a scoring system, in which we awarded 2 points for a perfect match (word for word match), 1 point for a partial match (an item was not a word for word match), and no points for an incorrect match (an item completely divergent from the original entry in the trial registry) for each of the 11 items. Three authors (PW , PG, and AP) assigned scores independently to each article. If there was a difference in the score (0/1/2) assigned among them, this was resolved through discussion with all other authors to reach a consensus. Thus, the maximum possible score for each paper was the number of items multiplied by 2, i.e., 22.

Descriptive statistics were used for data analyses. Quantitative data were expressed as median and range and categorical data as proportions.

RESULTS

Demographics

A total of 75 RCTs were published in JAMA in 2013. We included 74 RCTs as we were unable to trace the registry entry of one paper.

The 74 RCTs covered 10 therapeutic areas which included cardiovascular (n = 22), maternal and child conditions (n = 11), critical care (n = 9), respiratory illnesses (n = 7), infectious diseases (n = 7), psychiatric conditions (n = 4), orthopedic conditions (n = 3), gastrointestinal disorders (n = 3), endocrine and metabolic disorders (n = 3), and miscellaneous (n = 5).

The median (range) total score achieved by the RCTs was 15.[7-19] When expressed as a percentage (%), the median (range) (interquartile range) was 68.2 (31.8–86.4) (59.09–72.72) indicating that none of the RCTs achieved a perfect score of 22 (100%). Figure 1 is a box-and-whisker plot showing the distribution of scores.

Data set items analysis

Table 1 summarizes the details of the 11 data set items matched for content between registry entry and publication.

Only 13.5% of the RCTs were a perfect match with their registry entries in terms of title while the rest were an incorrect or partially correct match. For example, the title of an RCT as mentioned in the registry was "Targeted and Tailored Messages to Enhance Depression Care" whereas that in the published article was "Patient Engagement Programs for Recognition and Initial Treatment of Depression in Primary Care: A Randomized Trial."[9]

The primary and secondary objective had an exact match with the registry entry in only 12% and 76% articles, respectively. One RCT registry entry described the primary objective to be "To determine whether the microbiological efficacy of the mixture formulation consisting of ciprofloxacin for inhalation and free ciprofloxacin for inhalation is superior to placebo for inhalation in the treatment of patients with noncystic fibrosis (non-CF) bronchiectasis" whereas the published article mentioned "To evaluate the clinical efficacy and antimicrobial resistance cost of low-dose erythromycin given for 12 months to patients with non-CF bronchiectasis with a history of frequent pulmonary exacerbations" as the primary objective.[10]

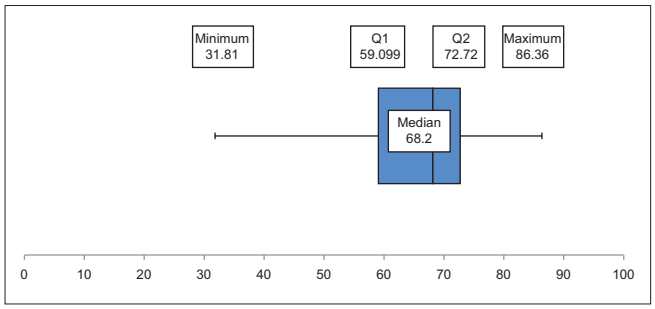

Figure 1: Box-and-whisker plot of total percent scores among the randomized controlled trials (*n* = 74)

Over half of the articles did not match in study type with their registry entry, and almost three-quarters did not match perfectly in the inclusion and exclusion criteria. For example, an RCT evaluating the effect of providing incentives to small clinics on their performance; the registry mentioned it to be prospective observational case–control study while the publication mentioned it as a cluster randomized trial.[11]

About one-fourth of the articles showed some discrepancy in the age groups, half were different in the details in the "follow-up" and over one-third in the sample size. For example, the RCT "Thalidomide in Pediatric Inflammatory Bowel Diseases" targeted a sample size of 84 in the registry while the number enrolled as mentioned in the published article is 56.[12] No explanation for this difference is given in the publication.

Less than half scored a perfect match when the primary outcome was compared while 13.5% showed a perfect match while reporting the secondary outcome. For example, the registry entry of the RCT evaluating the effect of "Soy protein isolate supplementation on biochemical recurrence of Prostate Cancer after Radical Prostatectomy," mentioned nine secondary outcomes (isoflavone uptake, steroid hormone axis, serum cholesterol, thyroid activity, apoptotic activity, angiogenesis, oxidative stress, equol production, and insulin-like growth factor axis) which are not mentioned at all in the publication.[13]

We found only 14/74 (19%) published papers reported that changes were made after the process of registration along with reasons for these changes.

DISCUSSION

The present study evaluated content in published RCTs (which covered a diverse range of therapeutic areas) in JAMA over a 1-year period (2013) and matched it with the information present in the trial registry where the study was registered and found that none of the 74 RCTs achieved a 100% match for

Table 1: Data set analysis: Number (%) of randomized controlled trials receiving 0, 1, 2 points, respectively, for the 11 data set items of *n*=74 randomized controlled trials

Data set items (*n*=11)	Number of RCTs/74 (%) that were a perfect match	Number of RCTs/74 (%) that were a partial match	Number of RCTs/74 (%) that were an incorrect match
Title	10 (13.51)	60 (81.08)	4 (5.41)
Primary objective	9 (12.16)	60 (81.08)	5 (6.76)
Secondary objective	56 (75.68)	8 (10.81)	10 (13.51)
Study type	36 (48.65)	37 (50)	1 (1.35)
Inclusion criteria	20 (27.03)	53 (71.62)	1 (1.35)
Exclusion criteria	17 (22.97)	49 (66.22)	8 (10.81)
Treatment age group	54 (72.97)	7 (9.46)	13 (17.57)
Follow-up	34 (45.95)	19 (25.67)	21 (28.38)
Sample size	48 (64.87)	15 (20.27)	11 (14.86)
Primary outcome	33 (44.60)	34 (45.94)	7 (9.46)
Secondary outcome	10 (13.51)	53 (71.62)	11 (14.87)

RCTs=Randomized controlled trials

the information indicating there is a difference between what is registered and what is eventually published. There was a wide variability in the scores obtained by the papers ranging from 30% to 90%. Given that 74/75 RCTs were found registered, the ICMJE call for mandatory trial registration has been largely adhered to.

Of the individual data set items, the largest proportion of studies reported secondary objectives, study type, treatment age group, follow-up, sample size, and primary outcomes fully correctly while the largest proportion of studies reported study title, primary objective, study type, inclusion and exclusion criteria, and primary and secondary outcomes partially correctly. Only a small proportion reported all of the items totally incorrectly compared to what was planned and registered in the trial registry.

Several studies have examined different data set items and observed similar findings. It is well accepted that the sample size of any study should be planned a priori. We found as many as 35% of articles in our study set reporting a sample size different from that originally registered. Like our observations, Charles *et al*.[14] reported that sample size calculations were explicitly discrepant with the registered protocol in 30% of the articles they analyzed while Walker *et al*.[8] found a discrepancy in 60% in British Medical Journal and 58% in JAMA RCTs they reviewed. One possible explanation for the divergent sample size is that the original difference anticipated between the two treatment arms was based on an erroneous assumption and therefore led to a change. If the sample size is altered a posteriori, this should be explained in the publication as to why there was a change.

The primary and secondary outcome measures impact the practice of evidence-based medicine and are the pivotal findings of any study. We found that more than 50% of the RCTs in our study were either partially or totally incorrect in reporting these although this was more obvious in the secondary outcomes. Other authors have similar findings. Thus, Mathieu *et al*.[15] ($n = 323$ RCTs) and Ewart *et al*.[16] ($n = 110$ RCTs) found that 31% of RCTs studied by them had changes in the outcomes reported. Similarly, Walker *et al*.[8] ($n = 40$ from BMJ and 36 RCTs from JAMA) found a discrepancy in 47% RCTs in BMJ papers and 19% in JAMA. Just like our study, Ewart *et al*.[16] found more trials (70%) discrepant with respect to reporting of secondary outcomes. Such alterations can have substantial implications in the interpretation of trial results and raise doubts about the validity of the conclusions derived from the trial leading to publication bias.[17] The ClinicalTrials.gov initiative of making reporting of basic results mandatory is an important step toward minimizing this bias.[18]

A Cochrane review of 16 studies (assessing a median [range] of 54 [2–362] RCTs) comparing registries versus publications concluded that discrepancies between registries/protocols and published papers were common.[19] Importantly, this paper mentions that explanations for the changes are not stated in the published RCTs indicating lack of complete transparency in reporting results and diminishing the value of registering the trial before recruitment of the first participant. CONSORT 2010 guidelines[6] mention in subitem 3b and 6b that any change made to the trial protocol after study initiation must be reported in the final publication along with reasons for the same, and we found this in only 19% of published papers indicating nonadherence to an important subitem of CONSORT.

The difference between our paper and other papers in this area of investigation lies in the fact that we looked at 11 data set items while other studies have focused on fewer data set items such as objectives or sample size alone. There are currently twenty items in the WHO Trial Registration Data Set.[20] Of these, we chose only 11 data set items that we felt addressed the science of the paper, and this is a limitation of the paper. We thus left out Primary Registry and Trial Identifying Number, Date of Registration in Primary Registry, Secondary Identifying Numbers, Source of Monetary Support, Primary Sponsor, Secondary Sponsor, Contact for Public Queries, Contact for Scientific Queries, and Recruitment Status. We thus missed out on assessing certain aspects such as whether the trials were registered before enrolling the first subject or retrospectively and whether publication bias was associated with sponsorship of trials, which other studies have evaluated.[15,21,22] In addition, the study is limited by the fact that only RCTs from a single journal over a period of only 1 year were examined.

The process of trial registration has moved, over the years, from being ignored to becoming obligatory. However, its implementation remains fraught with challenges. It is the shared responsibility and scientific and ethical imperative of authors, sponsors, and editors to ensure adherence to CONSORT guidelines. Our findings also suggest that editors and peer reviewers do not take advantage of the fact that registry data are available for easy cross-checking and can allow them to take better decisions regarding the publication of the submitted manuscript and if necessary, seek explanation from authors.

CONCLUSION

Compulsory registration of RCTs loses its objectives of transparency and accountability when the content of registry information does not match the final publication, and our study shows that this is an ongoing phenomenon.

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Conflicts of interest

There are no conflicts of interest.

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