

Agreement of Primary Outcomes in Chiropractic-Related Clinical Trials Registered in clinicaltrials.gov with Corresponding Publication.

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Abstract

Introduction:

Previous analysis of registered clinical trials has found a disappointing number of study protocols result in publications which change what the registered a priori primary outcome measure is. Likewise, there is a disappointing rate of unpublished trials. Similar research has not been published on chiropractic-related studies. Primarily this investigation determined if reported primary outcomes in chiropractic-related clinical trials registered in clinicaltrials.gov match their published results. Secondly, other outcome measures and publication status are assessed.

Methodology:

Clinicaltrials.gov was searched for chiropractic-related trials, using the search terms “chiropractic”, “chiropractor”, and having a completed status. Publication status was determined by searching PubMed (pubmed.gov), Index to Chiropractic Literature (chiroindex.org), and Google Scholar (scholar.google.com) through 29 May 2020. If the study was published, outcome measures were compared between the clinicaltrials.gov entry and the published paper to assess for consistency by two independent investigators. If there was disagreement between investigators, a third evaluated the data and decided if the published paper agreed with the clinicaltrials.gov entry.

Results:

Within clinicaltrials.gov 171 chiropractic-related protocols were identified. Twenty-five (25) had results posted and 102 were published. Twenty-nine of those entries produced multiple papers consisting of protocols, plot/feasibility studies, clinical trials, and poster presentations. Of the 102 studies published, 92 (90.2%) had agreement between their primary outcome and the listed entry on clinicaltrials.gov and 82 (80.4%) agreed with the secondary outcomes in the registered protocol.

Entries on clinicaltrials.gov had a 59.6% (102/171) publication rate and a 14.6% (25/171) rate of displaying their results.

Conclusion:

A modest rate of agreement (90.2%) between clinicaltrials.gov entries and the 102 published papers (59.6% publication rate) were found. While chiropractic-related clinical trials are fewer in number compared to medical trials, chiropractic-related research has a substantially better rate of primary and secondary outcome concordance with registered protocols and a better publication rate.

Investigators need to continue to upload results onto clinicaltrials.gov and seek publication regardless of the study findings. It is important to publish negative results so as not to introduce publication bias into systematic reviews and meta-analyses. Both positive and negative findings are important when evaluating treatments and determining the best care for patients.

Introduction:

Clinical trial registries are an important tool in evidence-based medicine to monitor selective reporting of outcome measures, publication bias and duplication of trials. In addition, they establish records of non-published trials for clinicians and researchers who are interested in investigating similar hypotheses. Trial registration is required in the United States via the Food and Drug Administration Modernization Act¹ and the Food and Drug Administration Amendments Act². Biomedical journals that subscribe to publication standards of the International Committee of Medical Journal Editors (ICMJE)⁴ require that clinical trials are registered. Finally, the World Health Organization⁵ also requires trial registration.

In an analysis of registered clinical trials in medical research Fleming and Goldacre⁵ have found that a disappointing number of study protocols resulted in publications which change the registered *a priori* primary outcome. Likewise, there is a disappointing rate of unpublished trials. Huić, Marušić, and Marušić⁶ evaluated randomized control trial (RCT) completeness and agreement between clinicaltrials.gov and ICMJE publications which found comparable findings to Fleming and Goldacre. Similar research on changing primary outcome measures has not been published on chiropractic-related studies, that we are aware of. The primary purpose of this investigation was to determine if reported primary outcomes in chiropractic-related clinical trials registered in clinicaltrials.gov match their published results. Secondarily, other outcome measures and publication status are assessed.

Methodology:

Clinicaltrials.gov was searched for chiropractic-related trials, using the search terms “chiropractic”, “chiropractor”, and having a completed status. Publication status was determined by searching PubMed (pubmed.gov), Index to Chiropractic Literature (chiroindex.org), and Google Scholar (scholar.google.com) through 29 May 2020. Search terms for these included the official trial name, the entry name on clinicaltrials.gov, the National Clinical Trial (NCT) identifier, or searching for the principal investigator (as an author [au] search). If the study was published, the paper was acquired and outcome measures were compared between the clinicaltrials.gov entry and the published paper to assess for consistency which was determined by two investigators (RMC, DSM) independently. If there was disagreement between those investigators that they could not resolve, a third investigator (SMP) broke the tie.

Results:

Within clinicaltrials.gov 171 chiropractic-related protocols were identified. Of these protocols, 160 novel entries were found with the search term “chiropractic” and 11 novel entries were found with “chiropractor”. Twenty-five had results posted on clinicaltrials.gov and 102 were published. Twenty-nine of those entries produced multiple papers consisting of pilot studies, feasibility studies, protocol papers, clinical trials, mixed-methods trials, and poster presentations.

Of the 102 studies published, 92 (90.2%) had agreement between their primary outcome and the listed entry on clinicaltrials.gov and 82 (80.4%) agreed with the secondary outcomes on the listed site. Seven of

those were poster presentations and we were unable to find these studies published in a peer-reviewed journal.

Completed trials on clinicaltrials.gov had a 59.6% (102/171) publication rate and a 14.6% (25/171) rate of displaying their results on the website. Eighty-four of those published were from 2016 and earlier and the remaining eighteen were after 2017.

Table 1

below shows by year, the number of protocols on Clinicaltrials.gov that were registered and published. During the period of the study, 171 total protocols were registered and 102 (60%) were published.

	Number of protocols registered year	Number of studies published per year
2001	3	0
2002	1	1
2003	2	0
2004	1	1
2005	8	1
2006	20	0
2007	22	2
2008	17	6
2009	13	7
2010	10	13
2011	7	4
2012	13	7
2013	12	6
2014	10	12
2015	9	12
2016	8	12
2017	5	7
2018	6	9
2019	4	1
2020	0	1
Totals	171	102

Table 1: Percentages of registered and published ClinicalTrials.gov Entries

Discussion:

A modest rate of primary outcome agreement (90.2%) between clinicaltrials.gov entries and the 102 published papers (59.6% publication rate) were found. This compares favorably to what Fleming and Goldacre⁵ and Huić, Marušić, and Marušić⁶ reported, that 38.8% and 64.5% of RCTs in medical literature had discrepant primary and secondary outcomes, respectively. Ramagopalan et al (2014)¹³ reported that 31.7% of registered interventional studies between 1999 and 2012 on clinicaltrials.gov had changed their primary outcome measure between the initial entry and obtaining a completed status. In a revision to the previous study, Ramagopalan, et al (2015)¹⁴ looked at completed interventional studies between 1999 and 2014 that had results published on clinicaltrials.gov and reported that 92.5% of those studies changed their primary outcome measure between initial entry and obtaining a completed status. While these two papers do not assess agreement between the clinicaltrials.gov entry and a published paper, it does demonstrate a large proportion of them were not consistent with their initial goal. The authors of those papers attributed this to industry funding and reporting of statistically significant outcomes. Fleming and Goldacre⁵ reported a 44.4% publication rate of trials registered in clinicaltrials.gov and the European Union Clinical Trials Register.

Compared to what we found in the literature, chiropractic-related human subjects studies show a better primary outcome agreement and publication rate. Why chiropractic research has a better agreement and publication rate than the biomedical research community writ large is not explained in the data. We believe that this may be due to two factors. A significant research effort in the chiropractic profession is relatively recent^{7,8,9,10} and thus likely to have learned from advances made in the overall biomedical research community. For a, so-called marginal profession¹¹ there is an imperative to do better than the overall community.

A study by Wells and Lawrence¹² found bias in chiropractic-related publications and spoke to a need for more investigators to add results to clinical trial registries. Our study found more “chiropractic” studies than Wells and Lawrence when searching the same database (160 vs. 65). Wells and Lawrence searched for the terms “chiropractic” (data collection ended in Aug 18) and “spinal manipulation” (data collection ended in May 19), while we searched for “chiropractic” and “chiropractor”. Additionally, they searched for all registered protocols, not just completed entries. The data collection time periods and different search methods may account for the differences in entities found.

Unfortunately, only 14.6% (25/171) studies had included results on clinicaltrials.gov. One purpose of clinicaltrials.gov is to have a database of results from clinical trials that have and have not been published, so without posted results from these protocols, the information they obtained is lost. This leads to more publication bias and loss of clinical information. It is important to note, 13 of the unpublished entries on clinicaltrials.gov were recent (within the last three years) and may be still seeking publication at the time of this investigation.

Conclusion:

To date, we found one previous study¹² that has evaluated chiropractic's publication rate and no chiropractic studies assessing outcome agreement in a clinical trial registry. To further build upon the knowledge base for this manual healthcare, more of chiropractic-related clinical research needs to be completed.

While chiropractic-related clinical trials are fewer in number compared to medical trials, chiropractic-related research has a substantially better rate of primary and secondary outcome concordance with registered protocols and a better publication rate. A possible explanation for this is that funding for chiropractic studies is comparatively sparse and authors of these studies are ambitious to report findings, whether positive or negative. They likely do this in an attempt to reduce bias and provide evidence on treatment effectiveness or ineffectiveness.

As other authors^{5,6,12,13,14} have reported, completion status and errors in registry information is common in healthcare research; it is encouraging that we found moderately good agreement in outcome measures with registered protocols. Investigators need to continue to upload results to clinical trial registries and seek publication regardless of the study findings. In general, it is important to publish negative results so as not to introduce positive bias into meta-analyses. Both positive and negative findings are important when evaluating treatments and determining the best care for patients. Additionally, the NCT identifier should be included in published papers to better link with the clinical trial registry.

Abbreviations

RCT

randomized control trial

ICMJE

International Committee of Medical Journal Editors

NCT

National Clinical Trial

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in its supplementary information files.

Competing interests

SMP is an associate editor of *Chiropractic and Manual Therapies*. He was not involved in or had any influence over the review process or the decision to publish. None of the remaining authors have any competing interests to declare.

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Authors' contributions

RMC obtained and analyzed the data and wrote the manuscript. DSM analyzed the data and made editing contributions to the manuscript. SMP analyzed the data and made final editing contributions to the manuscript. All authors read and approved the manuscript.

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Supplementary Files

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- [CotePerleMartin.PrimaryOMmatch.Dataset.July2020.xlsx](#)