International Journal of Cardiology 227 (2017) 299–304

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The heart of the matter: Outcome reporting bias and registration status in cardio-thoracic surgery

Jordan Wiebe *[,1], Grant Detten [1], Caleb Scheckel [1], David Gearhart [1], Denna Wheeler [1], Donald Sanders [1], Matt Vassar [1]

Oklahoma State University Center for Health Sciences, USA

ARTICLE INFO

Article history:
Received 4 August 2016
Accepted 6 November 2016
Available online 8 November 2016

Keywords:
Published outcomes
Registered outcomes
Trial registration
Randomized clinical trials (RCTs)

ABSTRACT

Background: Our objective is to compare registered outcomes to published reports; to evaluate for discrepancies favoring statistically significant outcomes; to examine funding source and likelihood of outcome reporting bias; and to evaluate for any temporal trends in outcome reporting bias.

Methods: PubMed was searched for randomized controlled trials published between 2008 and 2015 from 4 high impact cardio-thoracic journals: *European Journal of Cardio-thoracic Surgery* (EJCS), *The Journal of Cardiothoracic Surgery* (JCS), *The Journal of Thoracic and Cardiovascular Surgery* (JTCS), and *Annals of Cardiothoracic Surgery* (ACS). Data was collected using a standardized extraction form.

Results: We reviewed 287 articles, of which 214 (74.6%) did not meet registration criteria. Of those 214, 94 (43.9%) were published in the EJCS, 34 (15.9%) in JCS, 86 (40.2%) in JTCS, and 0 (0%) in the ACS. Of the remaining 73 articles, 34 (46.6%) had a discrepancy between the primary outcome registered and the published outcome, and 11 of the 34 reported p-values favoring the change. We also found that 12 of the 73 registrations had updated primary outcomes from the initial report to the final report. The timing of registration was an incidental finding showing 14 (19.1%) articles retrospectively registered, 29 (39.7%) registered during patient enrollment, and 30 (41.1%) registered prospectively.

Conclusion: The results indicated that selective outcome reporting is prevalent in cardio-thoracic surgery journals. The more concerning issue, however, is the lack of registration or provision of registration number for randomized controlled trials within these journals.

1. Introduction

The clinical practice of surgery is based largely on published outcomes from randomized controlled trials (RCTs) and systematic reviews that synthesize research evidence. By defining specific outcomes, these reviews identify techniques and approaches that can improve patient morbidity and mortality. Clinicians use this information to formulate and administer care to their patients. Thus, biased research can lead to inefficient or harmful treatment [1]. Trial registration was introduced, in part, as a means to limit bias and promote greater transparency in results.

In July of 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a publication policy requiring all member journals to register all RCTs with a clinical trial registry prior to enrolling participants [2]. Since then, other leading medical editor groups, government mandates (e.g., 2007 FDA Amendments Act), and watchdog groups (e.g., COMPARE project) have reinforced this policy. Trial registrations describe the key elements of a trial, including the pre-specified primary and secondary outcomes. This permanent record helps limit the risk of selective outcome reporting that has been identified in previous clinical trials.

Selective reporting bias occurs when pre-specified outcomes recorded in a clinical trial registry or protocol are modified in the published report based on statistical significance, such as changing statistically significant secondary outcomes to primary outcomes (upgrading) or non-significant primary outcomes to secondary outcomes (downgrading) in the published report. This bias hinders clinical decision making, because clinically relevant risks and benefits may be under- or over-reported and may not be available to clinicians. Rates of selective reporting bias vary widely across clinical specialties. We investigate cardiothoracic surgery, a specialty in which little is known

* Corresponding author at: Oklahoma State University Center for Health Sciences, 1111 W 17th St., Tulsa, OK 74107, USA.
E-mail addresses: jordanewiebe@gmail.com (J. Wiebe), grantrd@okstate.edu (G. Detten), caleb.scheckel@okstate.edu (C. Scheckel), david.gearhart@okstate.edu (D. Gearhart), denna.wheeler@okstate.edu (D. Wheeler), dsande01@gmail.com (D. Sanders), matt.vassar@okstate.edu (M. Vassar).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.11.098
0167-5273/

about selective outcome reporting practices. We investigated whether high-impact cardiothoracic surgical publications follow ICMJE's more extensive policies to avoid selective outcome bias in published clinical trials. Specifically, our study has four primary objectives: to compare pre-specified registered outcomes to those in the published reports; to evaluate discrepancies that favor statistically significant outcomes; to examine relationships between funding sources and the likelihood of outcome reporting bias; and to evaluate temporal trends in outcome reporting bias.

2. Methods

We performed a methodological systematic review of the four cardiothoracic journals with the highest impact factor from 2008 to 2015. This study did not meet the regulatory definition of human subjects research according to 45 CFR 46.102(d) and (f) of the Department of Health and Human Services' Code of Federal Regulations [3] and was not subject to Institutional Review Board oversight. We consulted Li et al. [4]; the Cochrane Handbook for Systematic Reviews of Interventions [5]; and the National Academies of Science, Engineering, and Medicine's (previously the Institute of Medicine) Standards for Systematic Reviews [6] to ensure best practices regarding data extraction and management. To ensure reporting quality for systematic reviews, we applied items 1, 3, 5–11, 13, 16–18, and 24–27 from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [7] and the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines [8] for reporting descriptive statistics. Prior to initiation of the study, we registered this study with the University hospital Medical Information Network Clinical Trials Registry (registry number R000025910UMIN000022483). All extracted data for this study are publically available on figshare (https://figshare.com/articles/CardioThoracic_Systematic_Review_Data_Extraction_Information_xlsx/3479585).

2.1. Eligibility criteria

We searched for RCTs indexed in PubMed between January 1, 2008, and December 31, 2015. We chose this period because it occurred several years after the ICMJE introduced the mandatory trial registration policy, and it allowed enough time to observe reporting trends in cardiothoracic journals. We included RCTs published in the *European Journal of Cardio-thoracic Surgery* (EJCTS), *Annals of Cardiothoracic Surgery* (ACS), *Journal of Cardiothoracic Surgery* (JCS), and *Journal of Thoracic and Cardiovascular Surgery* (JTCS). These journals are the top four ranked cardiothoracic journals, based on the most recent 5-year average impact factor reported in Journal Citation Reports. We used the National Institutes of Health's definition of a clinical trial: "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" [9]. We included RCTs, RCTs that used a crossover method, and follow-up studies on previously performed RCTs that analyzed different primary outcomes at a later time point but included follow-up data with the original data. The following article types were excluded: observational studies (including cohort, case–control, and cross sectional), meta-analyses, ongoing studies, commentary or discussion pieces, letters to the editor, articles with only a title or lacking an abstract, simulation-based studies, studies examining a mechanism, animal and in vitro studies, non-surgical studies, genetics studies, subgroup analyses, studies about medical students performing surgery, and studies examining pre-operation only.

2.2. Search strategy for identifying relevant studies

With the assistance of a medical research librarian, we conducted a PubMed search of the four previously listed cardiothoracic journals by limiting articles to "randomized controlled trials" between the aforementioned dates. The search was deployed as follows: ((“J Thorac Cardiovasc Surg”[Journal] OR “Ann Cardiothorac Surg”[Journal]) OR “J Cardiothorac Surg”[Journal]) OR “Eur J Cardiothorac Surg”[Journal] AND (Randomized Controlled Trial[ptyp] AND (“2008/01/01”[PDAT]: “2015/12/31”[PDAT])). The search took place on 5/20/2016.

2.3. Study selection and data extraction

Two investigators (J.W. and G.D.) independently screened the title and abstract of each citation for possible inclusion. Any disagreement about inclusion was resolved by consensus. Excluded citations were coded with the reason for exclusion as previously detailed. Investigators were blinded to registration status (whether the trial had been registered in a trial registry) during screening to minimize observer bias.

After screening, the citations were imported into the Systematic Review Data Repository (SRDR) of the Agency for Healthcare Research and Quality (AHRQ) [10] for data extraction. For internal calibration and to prevent discrepancies in extraction, each investigator underwent SRDR and data extraction training. First, investigators viewed training videos produced by the AHRQ on navigating the SRDR, creating an extraction form, and entering data (http://srdr.training.ahrq.gov/). Investigators next performed an AHRQ training exercise comprised of creating an extraction form and using it to enter data from one study. Investigators then completed a final set of training exercises, including an internally developed training video that explained this study's custom SRDR extraction form and data entry procedures.

Two investigators (J.W. and G.D.) independently reviewed the full-text articles for each study and extracted data using the SRDR. A subset of articles was cross-validated to improve the accuracy and efficiency of data extraction. Any disagreements were resolved by discussion between the investigators. A third-party reviewer (M.V.) was available for further adjudication. We extracted the following items from the published RCTs: primary outcome(s), secondary outcome(s), date of subject enrollment, trial registry database and registration number, timing of assessment of primary outcomes (e.g., pain at 12 h, mortality at 6 months), sample size, discrepancies between trial registration and publication as disclosed by the author in the publication, and funding source. We classified funding sources into the following categories: (1) private (e.g., Mayo Clinic or philanthropic), (2) public (e.g., government or university), (3) industry and corporate (e.g., GlaxoSmithKline), (4) university hospital, (5) mixed, or (6) undisclosed. For RCTs that reported multiple primary and secondary outcomes, we recorded each explicitly stated outcome. We interpreted the terms "primary," "main," and "key" as indicators of primary outcomes. If a primary outcome was not explicitly identified using these terms, we used the outcome stated in the sample size estimation. If sample size was not explicitly stated, we used the "number analyzed". If the article did not differentiate between primary and secondary outcomes, we coded these non-delineated outcomes as "unspecified" and accounted for them separately in the analysis.

The clinical trial registry or registration number was obtained for each published RCT, if stated, from the full-text review and data extraction. If a registration number but no trial registry was listed, then we searched Clinicaltrials.gov, the International Standard Randomized Controlled Trial Number Register, the World Health Organization's International Clinical Trial Registry Platform, and any country-specific clinical trial registry identified in the publication. The following characteristics were used to match the registered study to a publication: title, author(s), keyword, country of origin, sponsoring organization, description of study intervention, projected sample size, and dates of enrollment. When a publication did not explicitly state study registration information, the authors were contacted via email using a standardized email template inquiring about registration status. If after 4 days there was no reply, a second email was sent. If there was no reply within 1 week of the second email, the study was considered unregistered.

Each registered study was located within its respective registry. Two independent investigators (J.W. and G.D.) extracted the data. The following data were extracted using a standardized form on SRDR: date of trial registration; date range of subject enrollment; original primary registered outcome(s); final primary registered outcome(s); date of initial primary outcome registration; secondary registered outcome(s); sample size if listed; and funding source, if disclosed, using the previously defined categories. Although registration quality was not the focus of this study, registered trials lacking a clearly stated primary outcome and timing of assessment were not analyzed for outcome bias.

To be approved by the WHO, a trial registry must meet ICMJE criteria, including documenting any changes to that particular study's registry entries. If an included study had such changes, we recorded both the primary outcome from the time of initial registration and the primary outcome listed in the final registry entry. Unlike previous authors in this field of research, we included studies in WHO-approved registries that did not time-stamp the date of the initial primary outcome registration. Per the International Standards for Clinical Trial Registries section 2.4 [11], WHO-approved registries must time-stamp registry-approved changes to any registered trial, including data additions, deletions, and revisions. Therefore, if a WHO-approved trial registry did not display a history of changes, we recorded the date that the registry application was approved as the date of the initial primary outcome registration. Additionally, the listed primary outcome was recorded as both the initial registered and final registered primary outcome.

Investigators (J.W. and G.D.) then compared the primary outcome(s) listed in the publication to the initial registered primary outcome(s) for consistency. Decisions were made by consensus. Outcomes were deemed consistent if every primary outcome detailed in the publication was listed as such in the registry and vice versa. We defined five major discrepancies according to the classification system described by Chan et al. [12] and refined by Mathieu et al. [13]:

1. The registered primary outcome was reported as a secondary outcome in the published article.
2. The registered primary outcome was omitted in the published article.
3. A new primary outcome was introduced in the published article (i.e., a registered secondary outcome was changed to a primary outcome in the article or an outcome that did not appear in the registry was described as a primary outcome in the article).
4. The published primary outcome was described as a secondary outcome in the registry.
5. The timings of assessment of the registered and published primary outcomes differed.

Additionally, because trial registries allow authors to update their primary outcomes at any point, we also looked for matches between the original registered primary outcome(s) and published primary outcome(s). If the original registered primary outcome did not match the published primary outcome and changes were made after submission of the article, the study was flagged as having a discrepancy. If clarifying information about existing outcomes was added but no change was made to the registered primary outcome, the study was not flagged. Finally, we noted if an outcome was categorized as primary or secondary in the registry but was unspecified in the publication. These instances were not recorded as upgrades or downgrades, but the irregularity was recorded.

Articles with discrepancies that were found by using Mathieu et al.'s [13] system were also assessed to see if discrepancies favored statistically significant results. As with Mathieu et al. [13], a discrepancy was considered to favor statistically significant results