GUEST EDITORIAL

Mandatory trial registration in oral health research

Long overdue?

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The practice of evidence-based dentistry is based on the use of published scientific evidence to help dentists make clinical decisions. Knowing how to identify the best available evidence and factor it in to the clinical decision-making process is a fundamental skill taught in dental schools and continuing education courses across the globe. What if the best available evidence is biased? An epidemiologic study by Dechartres and colleages[1] published in a high-impact medical journal suggested that lack of prospective trial registration led to larger treatment effects. The need to control such bias is pertinent to the oral health research arena. This commentary will discuss updates in the regulatory requirements for trial registration and the importance of minimizing publication bias.

Publication bias was first discussed by Rosenthal,[2] who suggested that "For any given research area, one cannot tell how many studies have been conducted but never reported." This statement reflects that studies with positive findings are more likely to be published than studies with negative findings. Obviously, the term *positive finding* is used loosely herein as a relative synonym of *desired finding*.

Publication bias is no stranger to dentistry. The authors of a 2009 article found that among the major orthodontic journals, 9 of 10 articles reported positive findings.[3] A similar scenario was noted across top-impact dental specialty journals with registration data being rarely reported in trials published from 2008 through 2011.[4] Why is this important to oral health research? To decrease selective reporting of positive findings.

In an effort to minimize publication bias, the International Committee of Medical Journal Editors has mandated public trial registration,[5] and certain dental journals have embraced this requirement.[6,7] Public registries in which the public can freely search and access registered trials' records are available. One example is ClinicalTrials.gov, which is the largest and most well-known registry and results database. ClinicalTrials.gov is curated by the National Library of Medicine and holds over 200,000 study records.[5] The registry was originally established in response to the US Food and Drug Administration Modernization Act of 1997,[8] which required public registration of selected information for trials involving certain US Food and Drug Administration–monitored drugs and devices. In September 2016, the final rule for Clinical Trials Registration and Results Information Submission expanded these registration requirements to include relatively

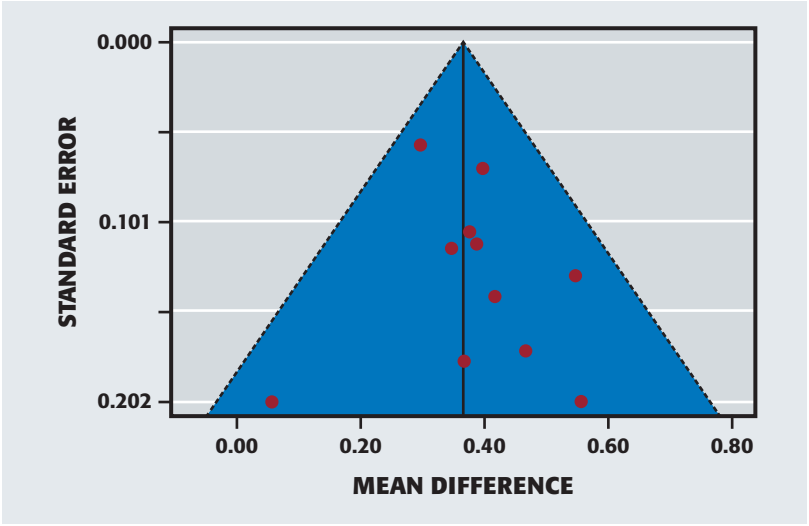

Figure 1. Typical example of a funnel plot from a meta-analysis in oral health research. A funnel plot is drawn by plotting the effect size in each study on the x-axis against a measure of precision of the estimate on the y-axis. Note that few studies with effect sizes near 0 are depicted, whereas most studies show large effect sizes. This is a typical example of publication bias; data were simulated and plotted with the "metafor" package in R statistical software (https://www.r-project.org/).

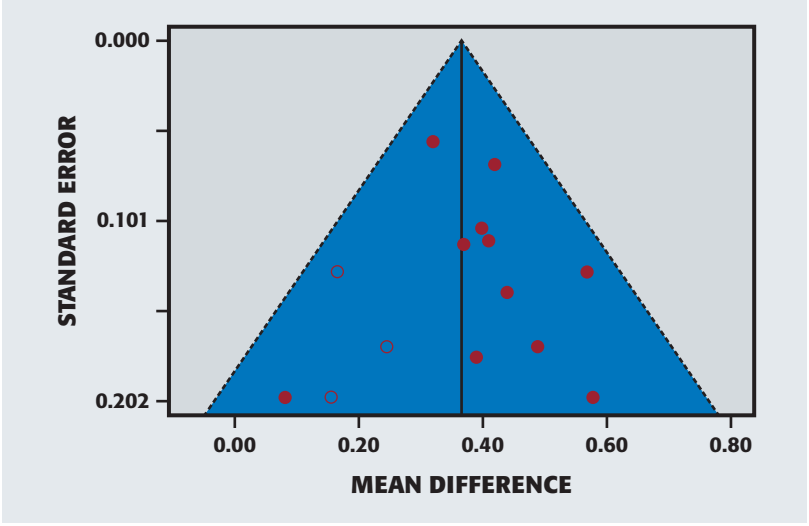

Figure 2. The same funnel plot as presented in Figure 1 has been augmented with additional points representing 3 "missing" studies (depicted by the open circles). The imputation was done using the "trim and fill" method.[11] This method is a data augmentation technique aiming to adjust for publication bias in funnel plots. The trim and fill approach complements the funnel plot with "missing" data points that make the funnel plot more symmetric.[11] In this example, the filled data points represent studies with small, near-zero effect estimates that are likely to be missing because of positive-outcome bias, as it often occurs in oral health research.

any clinical trial being performed in the United States or involving biologics, drugs, or devices manufactured in the United States.[9] This important development increases accountability on behalf of all responsible parties and will hopefully encourage publication of trials irrespective of the statistical significance, or lack thereof, of their results. Notably, the final rule emphasized the importance of timely reporting of summary trial results for every registered study.[9]

Misinformation due to publication bias becomes evident in systematic reviews. Systematic reviews hold the highest rank on the pyramid of evidence, and their results are used to shape clinical recommendations.[10] However, systematic reviews are inherently dependent on published information. Therefore, their results are compelled to skew toward the findings reported in the published body of literature. Consider 20 studies being performed to investigate the effect of a new periodontitis treatment adjunct and 19 of them failing to show a significant effect. If the only study being published is the one reporting a significant effect, then one can perceive the extent of misinformation associated to publication bias. An example of publication bias is discussed in Figures 1 and 2.[11] Evolving guidelines support the inclusion of what is referred to as "gray literature" to ascertain that existing studies with negative findings are discovered during systematic reviews and provide pragmatic effect estimates in meta-analyses, although this approach has been criticized as being inefficient.[12] Nonetheless, prospective trial registration and results reporting can fortify dental research against publication bias.[6,9] A trial's registry record serves as its fingerprint; it includes the study protocol, an annually updated record of recruitment status, summary of data obtained, and a blueprint for data analysis. The public availability of this information ascertains that the results of the study will be made public even if the researchers or sponsors decide against pursuing a peer-reviewed publication. Notably, it becomes evident that trial registration alone will not alleviate the issues associated with publication bias. Trial registration must be followed by annual updates and timely publication of a summary of study results to fullfill its role.[9]

Selective reporting is yet another facet of the ramifications of nonregistration. Selective reporting bias arises when information that was recorded is intentionally not reported, or when outcome switching occurs in light of unanticipated results. Dechartres and colleagues[1] reported that "From 43 meta-analyses (213 [randomized controlled trials]), trials registered after the primary completion date or unregistered tended to show larger estimates than those registered before (combined [ratio of odds ratio] = 0.84, 95% [confidence interval] 0.71-1.01)." A key difference between prospective public registration, post-hoc registration, or even nonregistration lies in knowledge about the pretrial hypothesis.[13]

Trial registration is important because it increases the chance of study results eventually becoming public, and it limits the risk of reporting chance findings as definitive study conclusions.

The first type of selective reporting, suppression of information, occurs when an outcome that was specified pretrial is omitted. Suppression of outcomes often arises owing to lack of significant findings or sponsor demands, as in the case of adverse events in trials involving drugs.[14] One of the main functions of mandatory registration is to eliminate selective reporting. Specification of the primary, secondary, and safety outcomes is a key component of prospective registration, and the public availability of this information minimizes the chance for data manipulation. However, post hoc registration or registration of a trial near completion negates any registration benefit related to minimizing selective reporting. In fact, it is well documented that the ersatz registration of studies retrospectively to satisfy journal requirements is equally likely to be associated to favorable findings as lack of registration is.[15]

Selective reporting may also arise when ranking of the outcomes is based in their results rather than their clinical relevance as defined during the study design. This act of "cherry picking" leads to spurious findings being reported as significant; such results are almost never reproducible (for example, http://compare-trials.org/ reports the ongoing findings of a research group investigating outcome switching in the top 5 medical journals). Data dredging or "*P* hacking," intensive outlier removal, or multiple testing are approaches that researchers sometimes use to make it past the infamous .05 mark, an arbitrary threshold for statistical significance.[13,16] Data dredging refers to the use of data mining techniques to identify any possible relationships between data without a priori defined hypotheses.[13] Evolving guidelines to reduce selective reporting necessitate that the primary outcome is defined at the time of registration along with information related to its specific measure and time points of assessment.[9] This is not to say that a trial could not report negative findings for the primary outcome and positive findings for a secondary outcome or an exploratory analysis. However, such findings of successive testing should be judged at a higher level of scrutiny and be definitively assessed in confirmatory studies before informing clinical decisions.

Taking everything into account, trial registration is important because it increases the chance of study results eventually becoming public, and it limits the risk of reporting chance findings as definitive study conclusions. The main purpose of registration of clinical studies is to prevent publication bias. To be effective, this measure also needs to be pragmatic. There are 3 key axes that direct the actions to achieve this goal: authors, editors and reviewers, and sponsors. Authors have an ethical responsibility to register trials before recruitment. This is a requirement for ethical approval by institutional review boards across the United States and is now expanding into other regions globally. Furthermore, editors and reviewers should be open to disseminating scientifically robust and impactful findings irrespective of their direction—positive or negative. A form of bias occurring at the editorial level is that of *selective review*, when trials showing small effects or negative findings are not allowed to undergo peer review. Admittedly, trials with positive findings are not only published more often but also more rapidly than trials with negative findings.[17] During the peer-review process, it is the responsibility of the reviewers to confirm that a trial has been prospectively registered and that the reporting of the study is concordant with the registered protocol. Last but not least, at the sponsor-investigator level necessary precautions need to be taken to ensure that funding agencies and for-profit organizations only serve as curators and do not interfere with the public availability of research data. There have been cases of industry sponsors suppressing unfavorable results of trials and in which legal actions were taken.[18] Importantly, the ramifications of public registration can ultimately better inform clinical decisions for the patient in our chair. ■

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