Negative Is Positive: A Plea to Publish All Studies Regardless of Outcome

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Abstract

Negative results from trials can be just as important as those which are positive. The results of all trials need to be made easily available to avoid biases when compiling the totality of the data. This is critical to ensure that guidelines and treatment standards are reflective of the "the truth, the whole truth, and nothing but the truth." Additionally, negative trial results avoid duplicative studies and may also contain important safety information that would otherwise be lost. Several outlets now exist for negative trials, but investigators and trial sponsors need to be encouraged or mandated to post the results of all trials, regardless of results, in the public domain.

Key words: Negative results, clinical trials, publication bias, clinicaltrials.gov

Positive results from clinical trials naturally get the headlines in the media and are published in more prestigious and higher-impact journals. But what about negative results? They also get published, but less frequently and with more delays.[1] In fact, many investigators abandon negative studies and focus their time elsewhere, leaving these bodies of work in the dark and unavailable, even in cyberspace. Worse yet, the omission of critical information such as safety data could be harmful to the general public, as has been documented in several noncancer areas.[2-4] There are no firm estimates on the imbalance of publication of positive versus negative cancer trials.

So why is it important to publish negative studies? There are many ways that the dissemination of trials that do not meet their primary endpoints can still help science advance and ultimately benefit patients. For one, ineffective and dangerous therapies that are often "tailored" in desperate situations would be avoided. Even animal studies cannot get approved by most Institutional Animal Care and Use Committees (IACUCs) without a literature search to show that the proposed experiments have not been conducted in the past; oddly enough, the same is not required of clinical trials. Secondly, when studies are pooled, or formal meta-analyses are conducted to obtain more definitive estimates of efficacy and safety, publication bias resulting from the omission of negative studies may artificially inflate the results.[5] This can lead to inappropriate guidelines and widespread adoption of costly and potentially harmful therapies. Finally, science builds on previous results—new directions require that all data be available. Biological hypotheses that lead to clinical investigations can develop from both positive and negative results.

In 2000, a federal law was passed that stipulated the development of the ClinicalTrials.gov website to provide information about clinical trials for serious medical conditions, with specific information about trial access and other details. In 2007, Congress enacted the Food and Drug Administration Amendments Act (FDAAA), in which Section 801 directed clinical trial sponsors to report primary outcomes of trial results within 1 year of final data collection, and to make this publicly available on ClinicalTrials.gov.[6] A recent analysis of 13,327 trials completed between 2008 and 2012 that met FDAAA criteria showed that only 13.4% of trials reported summary results within 12 months of trial completion.[7] However, it is possible that data quality checks and regulatory requirements have delayed reports, and it is hoped that this number will rise as trial sponsors become familiar with this process.

The library sciences have advanced with electronic searches and online availability of virtually all published material. The new field of "big data"—the use of artificial intelligence and data mining applied to vast archives of information—promises to yield new clues to the challenges of cancer biology and discovery of vulnerabilities that can be exploited for clinical gains. Therefore, this may be a perfect time for a public plea to publish every study ever conducted, regardless of results.

Is this achievable? Absolutely. While high-profile journals may elect to publish only positive findings (or highly relevant and large negative studies), smaller negative trials can be published in a growing number of specialty journals. The *Journal of Negative Results in BioMedicine*, launched in 2002, is dedicated to negative (as well as provocative and paradigm-changing) results and encourages such submission for peer review and publication.[8] In addition, there could be a publicly funded repository of negative

trials that is searchable. This may be challenging because of the time and expense involved in expert peer review and editing, but even a collection of deposited articles that are not peer-reviewed could be helpful.

Academic credit hinges on peer-reviewed articles, but clinical investigators should also be given credit for their work if it can only be published in this setting. Just as the FDAAA mandates the publication of results of key trials, private, nonprofit, and governmental funding agencies can similarly stipulate that all funded trials eventually be published in a publicly searchable database. Institutional Review Boards (IRBs) can likewise impose such requirements as a condition for protocol approval. These policies are clearly justified, as they are for the public good. They avoid the repetition of unproductive trials and create more robust literature archives that actually protect future patients and clinical trial subjects.

Bringing negative prospective clinical trials to light will require a "carrot-and-stick" approach. However, the payoffs are great. We will be able get a more realistic and rapid sense of what works and what does not. Clinical investigators will have more ample and reliable preliminary data and background to support their new concepts. Reviewers of protocols will likewise be able to meet their obligations to properly evaluate studies and only approve safe and promising protocols, or to suggest evidence-based modifications. The real winner is the public, and specifically our patients, who are understandably impatient with the time it takes to expand our knowledge and introduce meaningful innovations in cancer care.

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