One in Five Cancer Clinical Trials Is Published: A Terrible Symptom—What’s the Diagnosis?

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There was a time in the history of science when publications represented a completed body of knowledge that took many years (sometimes a lifetime), often by a single person, to compose. Newton’s *Principia* [1] and Copernicus’ *On the Revolutions of the Heavenly Spheres* [2] come to mind. Indeed, the idea of publishing incremental scientific observations, something which we would call journal articles today, only began when letters between scientists began to be reproduced in the press.

Today’s world of scientific publication is entirely different. It is increasingly difficult for medical oncologists to keep current with the generally incremental advances published regularly by well-known and well-respected medical journals. And yet, as Ramsey and Scoggins point out in this edition of *The Oncologist*, we may be struggling to keep up with information that represents only “the tip of the iceberg” [3]. Slipping beneath the surface is a wealth of unpublished data that might prove valuable to the cancer research community. We can only guess at its content.

While there are inherent methodologic limitations to the analysis undertaken by Ramsey and Scoggins, the possibility that fewer than one in five cancer clinical trials find their way to the peer-reviewed literature is thought-provoking and disturbing. Obviously a variety of reasons may underlie the failure to publish: flawed trial design, a failure to reach endpoints because of any number of problems (including inadequate accrual), negative results, and simple neglect on the part of the trial sponsor and the principal investigator. These problems, individually or in combination, may contribute to the failure to submit a manuscript for publication.

Ramsey and Scoggins hypothesize that a major reason for failure to publish is selection bias against trials that do not meet their endpoints and, indeed, the majority (57%–90%) of the published trials are positive [3]. But other factors aside from a negative result may defeat a trial and its publication. Among these most prominently is the failure to accrue patients. So, while about one in five cancer trials is eventually published, equally sad is the fact that half of the unpublished trials have failed to accrue and reach endpoints; this finding represents an indictment of the review process that allows poorly designed or low-priority trials to be initiated, or delays them past their point of relevance. The latter consideration is particularly relevant to the National Cancer Institute (NCI) Cooperative Groups, which routinely take 2 years or more to bring a trial from concept to active accrual.

Dilts and Sandler have studied accrual patterns in four NCI-designated Comprehensive Cancer Centers and have made some remarkable conclusions [4]. Nearly 60% of trials opened for 5 years had fewer than five patients enrolled at each site, and, for >20% of studies, not a single subject had been accrued. Looking at the bigger picture, of all NCI phase I, II, and III trials opened and closed between 2000 and 2007, only 50%–60% achieved minimal stated accrual goals. So, while perhaps only one in five cancer clinical trials is ever published, of those unpublished, a significant percentage probably died for lack of accrual. Which potential statistic is the sadder, the low publication rate or the low accrual rate? In truth, they both are, as neither should be true.

We should also acknowledge that investigators and sponsors also face the hurdle of finding a journal willing
to publish a negative, poorly designed, or inadequately accruing trial. Journals live and die based on their Impact Factor, and a journal filled with such data will not attract readership, citations, and advertisement. There is no current peer-reviewed publication for studies of “lower priority.”

An unexplored issue is the possible failure of industry to publish disappointing results. In the past 15 years, industry has become the dominant sponsor of new drug trials. While academic investigators are key contributors to most industry-sponsored trials, a growing number of phase II, and even phase I studies are multicentered, and the sponsor may be the only entity with access to the complete dataset. The sponsor may have very little incentive to publish a negative trial. In the absence of a sponsor’s commitment to publish the trial in a timely way, the academic collaborators may have no ready means of acquiring a complete dataset and submitting a manuscript. Importantly, major pharmaceutical companies have developed a commitment to placing negative clinical trials in the public domain, even going so far as to formalizing this requirement into their standard operating procedures. But a posting on a Website is not the same as a peer-reviewed publication, and the potential for publication bias works as strongly against a sponsor as an academic investigator.

Are there solutions? We believe that the NCI, its grantees, and its Cooperative Groups need to focus their efforts on trials of the highest priority; they need to streamline their trials’ review process and need to provide adequate reimbursement for these trials. In return, the publication record of the groups for both positive and negative trials, indeed for all trials, should be the major determinant of their continued funding.

And finally, there is a need for a new venue for publishing all well-executed trials that fail to meet positive endpoints: “negative” in a sense, but valuable nonetheless. Sometimes such trials are “posted” on the Internet, but their format is not searchable by PubMed, MEDLINE, MEDLARS, or commonly used search engines. The Oncologist is considering whether it should undertake the publication of a peer-reviewed, searchable venue for these trials [5]. We invite our readers to tell us whether such a resource would be worth the considerable effort and expense.

In recent months, The Oncologist has advocated for transparency with regard to conflict of interest on the part of authors [6, 7]. We now raise the largest barrier to transparency, the failure to publish, and the resultant bias in published information.

There is an obligation on the part of investigators and sponsors to publish in a peer-accepted public forum the results of trials to which cancer patients have contributed their precious time and well-being, and for some, their very lives, in the hope that such information will accelerate the research process and save lives in the future.

To do any less is a disservice to the science to which we ought to be committed and a dishonor to the patients to whom we should be dedicated.

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