

### Commentary: Publishing Cancer Clinical Trial Results: A Scientific and Ethical Imperative

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For calendar year 2007, approximately 50,000 patients were accrued to therapeutic clinical trials performed at cancer centers supported by the National Cancer Institute (NCI). Although large, this accrual statistic represents only a fraction of the total yearly accrual of cancer patients to treatment trials in the U.S., because a large number of such studies are performed outside major academic medical centers [1]. In light of this major clinical trials effort, the report by Ramsey and Scoggins in this issue of *The Oncologist* [2] provides disturbing data regarding the remarkably modest number of oncologic clinical trials published in the peer-reviewed literature. In the roughly 3–8 years following the availability—and subsequent requirement—for registration of all clinical trials in the National Library of Medicine’s database, ClinicalTrials.gov, only one in five clinical trials could be accessed as a full publication in PubMed.

As outlined by the authors, these data provide continuing support for the presumption of a strong bias toward the publication of “positive” results in the cancer clinical trials literature [3]. More importantly, however, and despite the limitations of the retrospective nature of the methodology employed (limited time frame following trial registration analyzed for publication, use of only PubMed citations as

evidence of publication, focus solely on studies registered in ClinicalTrials.gov), <6% of all industry-sponsored studies had been published over this time frame, and 75% of those had reached a “positive” conclusion. On the other hand, 59% of the clinical trials performed by NCI-supported clinical trials networks had been published over the same period of time, and half of those trials reported a “positive” result. The latter figure, furthermore, is consistent with an ongoing evaluation of the publication rate of >1,500 phase II and III clinical trials performed in 2000–2005 by NCI’s Cooperative Clinical Trials Groups.

The apparent lack of access to the final efficacy and toxicity data for cancer clinical trials from all sponsors, but especially for industry-sponsored studies, poses multiple scientific and ethical questions. In the period 1959–1987, when the Division of Cancer Treatment at the NCI was the predominant sponsor of clinical new drug trials worldwide, the NCI supported peer-reviewed publications (*Cancer Chemotherapy Reports* and its successor, *Cancer Treatment Reports*) that were specifically devoted to the dissemination of cancer clinical trials results, both positive and negative, that frequently reported the outcomes of studies NCI was, itself, sponsoring. With the remarkable growth of

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cancer drug development activities outside the NCI, and in particular with the growth of studies of targeted cancer therapeutic agents developed by both large pharmaceutical firms and the biotechnology industry, and concomitant with the demise of the NCI's own clinical trial publications, access to peer-reviewed, "negative" clinical trial results has contracted dramatically. From a scientific and medical practice perspective, this is particularly difficult in light of the need to make clinical trial outcomes rapidly available to the cancer clinical trials community. For example, the recent U.S. Food and Drug Administration (FDA) MedWatch alert regarding the appearance of microangiopathic hemolytic anemia in patients treated in a clinical trial combining bevacizumab and sunitinib [4] strongly suggests that as experience mounts with the use of targeted anticancer agents in combination, unexpected toxicities are likely to be uncovered during clinical trials sponsored by industry as well as the NCI. It is a clinical and ethical necessity that both the efficacy and toxicity results of such trials become available expeditiously to the entire oncology community in the peer-reviewed literature.

In addition to the clear requirement for rapid dissemination of clinical trial outcomes, the report by Ramsey and Scoggins provides important additional insights into the larger cancer clinical trials endeavor in the U.S. during the past decade. Over half of the trials analyzed in their study were phase II investigations, but only 17.3% of these phase II studies had been published at the time of their evaluation. Of the nonrandomized trials evaluated in this paper, <5% were published. As discussed in detail elsewhere [5–7], changes to the phase II cancer clinical trials paradigm are under vigorous discussion with respect to the utility of adaptive and/or randomized designs, the requirement for larger sample sizes, and the applicability of pharmacodynamic endpoints. What is not a matter of discussion is the lack of utility of underpowered phase II investigations, in particular when the toxicity results inherent in those trials

are not available for potentially more insightful analyses of pooled clinical trial datasets.

The results outlined by Ramsey and Scoggins support the premise that the reporting of the outcomes of cancer clinical trials has been limited, even following the development of requirements for clinical trial registration by ClinicalTrials.gov. In response to the recognition of the limited availability of these data, the Clinical Trials Working Group of the NCI's National Cancer Advisory Board proposed that the NCI develop its own clinical trials database to capture all of the administrative and outcome data for the entire set of clinical intervention studies that are performed at NCI-supported institutions [8]. The initial effort to develop this database has now reached the pilot phase of implementation; by July 1, 2009 protocol accrual information will be reported on a quarterly basis from all NCI-designated cancer centers [9]. This effort has occurred in parallel with the passage of the FDA Amendments Act (FDAAA) of 2007 [10]. The FDAAA, in its initial phase, makes registration of all clinical trials in the U.S. with ClinicalTrials.gov a legal requirement with specific financial penalties for non-compliance. Over the next several years, the reporting of clinical trial outcomes within a specified time frame after trial completion will also be required. NCI's effort will complement that required by the FDAAA, because outcomes information will be reported during the course of clinical trials, rather than at their completion. It is likely, therefore, that over the next 5 years—by a variety of mechanisms—the oncology community can once again look forward to the rapid availability of critical safety and effectiveness information regarding new therapeutic cancer interventions. The rapid accessibility of this information is long overdue and should lead both to better planning for cancer clinical trial implementation by clinical investigators and broader treatment choices for cancer patients nationwide.

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