Researchers Left To Guess at Outcomes of Most Cancer Clinical Trials

By Renee Twombly

Medical literature, in general, and clinical trials of depression and cardiovascular disease, in particular, suffer from selective publication—studies published in journals tend to be overwhelmingly positive.

But the situation for cancer clinical trials has not been clear. Some small studies have hinted at publication bias, but now that a public clinical trial registry exists, two researchers from the University of Washington performed a simple analysis to get a more definitive answer. They matched trials registered at the National Institutes of Health’s clinicaltrials.gov with subsequent publication of results.

They found that not only were published cancer clinical trials largely positive, but that results for most of the registered trials were nowhere to be found.

In the September 24 issue of The Oncologist, Scott Ramsey, M.D., Ph.D., an internist at the Fred Hutchinson Cancer Research Center, and his postdoctoral researcher, John Scoggins, Ph.D., say that of the 2,028 studies of cancer treatment registered on the database, only 17.6% of the trials were eventually published in peer-reviewed medical journals. And of these published studies, nearly two-thirds reported positive results, meaning that the study treatment worked as researchers had hoped.

“Publication bias does appear to be a problem in clinical cancer trials, but what this study really documents is that almost all trials—four of five—never reported any results,” said Ramsey. “The question is what is it about those trials that resulted in them not being published? Was it because they never got completed? Was it because the results were negative or harmful to the interests of whoever sponsored them? Did someone just get lazy and not bother to write up, then publish it?”

“The problem, to me, is that even failed trials contain information,” he said. “If we don’t have any record of why the trial failed, or what happened that led to it failing, then we miss out on a lot of important information. It’s like practicing on the tip of an information iceberg.”

This is clearly a major ethical issue, said Jeffrey Peppercorn, M.D., assistant professor of Medicine at Duke University Medical Center. Peppercorn published a 2007 study in Cancer that found that industry-associated cancer research publications were overwhelmingly positive compared with research that was not supported by industry—one of the first to document such bias in cancer studies. “Part of the contract we make with our patients when they agree to participate in a clinical trial is that we will use the results to improve our scientific knowledge and the care of future patients. Failure to publish the results of a trial, or design and conduct a trial that does not yield results, positive or negative, that can be used to improve our understanding, violates this important principle.”

Without Results, Patients at Risk

Ramsey’s study, which he says was a quick analysis that may suffer from several limitations, is nevertheless one of the first to examine the fate of trials listed on the NIH Web site, which was developed in collaboration with the U.S. Food and Drug Administration as a result of the FDA Modernization Act of 1997. This was a first step toward increasing transparency in clinical trials, and since its 1999 inception, researchers have been able to choose to list the details of clinical trials on the Web site. In 2004, however, the International Committee of Medical Journal Editors initiated a publication policy that requires investigators to register their trials at the site before enrolling patients. All trials registered in clinicaltrials.gov receive a unique identifier, and since September 2005, the journal editors committee has recommended that published results of registered clinical trials identify that unique tag.

In September 2007, Ramsey and Scoggins downloaded the contents of the registry (44,232 trials) and searched for clinical trials that focused on cancer treatment and were designated as either completed or terminated. They found 2,028 trials that met their inclusion criteria. They then checked whether researchers had listed publications on the registry site or in the National Library of Medicine’s PubMed database that included the unique registry identifier. The researchers found that 17.6% of studies—roughly one of five that were registered—were listed as published.

Further analysis showed that terminated trials had a lower publication rate (3.4%) than that of completed trials (19.5%). Trials that described procedures had the highest proportion of publications (25.7%) compared with drug trials (17.4%). Phase III trials were more likely to be published (26.3%) than other phases, including phase IV studies (14%).

The researchers also found that studies sponsored primarily by networks (consortia of medical research organizations) were the most likely to be published (59%), whereas industry-sponsored trials were the least likely to be published (5.9%). University and research organizations made up the largest proportion of primary sponsorship for registered studies (42.1%), and nonrandomized trials were much less likely to be published (4.4%) than randomized trials (19.6%).

Ramsey and Scoggins then looked at publication bias in the 357 trials that were published and could judge positive versus negative results in 341 studies. Among these, 220 (64.5%) reported positive results. NIH-sponsored trials reported the highest percentage of positive abstracts (78.8%) and networks reported the lowest (50%).

Ramsey said that these findings may be imperfect because only trials registered at clinicaltrials.gov were considered, although there are other, much less comprehensive
sites where researchers can list their trials. Also, he and Scoggins relied on the presence of the unique identifier to locate published results and did not consider published abstracts presented at national meetings. Nonetheless, Ramsey said that although there may be understandable reasons why researchers and sponsors fail to publish clinical trials—authors may view negative results as not advancing medical care or their careers, or as difficult to find a journal to publish them in—he argues that publication of negative clinical trials “clearly has value to researchers and patients.”

“Researchers benefit from not repeating a negative trial and from what the negative trial implies regarding the treatment and outcome,” he said. “Unpublished trials may also have special importance in oncology because of the toxicity and/or expense of many therapies.”

“If selective publication has altered the apparent risk–benefit assessments of cancer treatments, doctors and their patients may not be making treatment decisions that are in their best interest,” he said. “Without that information, we are putting people at risk for getting therapies that aren’t going to help them or for giving them things that might be hurting them,” he said.

Designing Solutions
Whereas Ramsey and Scoggins hypothesize that a major reason for selection bias is a failure to publish trials that do not meet their endpoints, two editors of The Oncologist offer a different perspective in an editorial that accompanies Ramsey’s study. Senior Editor Gregory Curt, M.D., and Editor in Chief Bruce Chabner, M.D., say that failure to accrue patients is a major reason that clinical trial results are not published, and they add that this is a particular problem among National Cancer Institute cooperative groups.

They say that half of the unpublished trials have failed to reach endpoints because they failed to accrue enough patients and that this 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.”

“When potential statistic is sadder, the low publication rate or the low accrual rate?” asks Curt, a researcher at AstraZeneca, and Chabner, a professor at Harvard Medical School who was a longtime director of the National Cancer Institute’s Division of Cancer Treatment.

Backing up their assertion are studies that have found that NCI cooperative groups routinely take 2 years to bring a trial from concept to active accrual, that nearly 60% of such trials opened for 5 years had fewer than five patients enrolled at each site, and that in more than 20% of the studies, not a single subject had been accrued. They also say that of all NCI phase I–III trials opened and closed between 2000 and 2007, only 50%–60% achieved minimum stated accrual goals.

Publishing under these circumstances is difficult, they say. It poses a hurdle to find a journal willing to publish a negative, poorly designed, or inadequately accruing trial.”

The authors offer several solutions. One is that the NCI, its grantees, and its cooperative groups need to focus their efforts on trials of the highest priority. NCI needs to streamline their trials’ review process to eliminate future poorly designed trials and provide adequate reimbursement to see trials through. In return, the publication record of the groups for both positive and negative trials should be the major determinant of their continued funding, they say.

Curt and Chabner also say a new venue is needed for publishing all well-executed trials that fail to meet positive endpoints, and they say that The Oncologist is considering whether it should undertake the publication of a peer-reviewed, searchable venue for these trials. “We now raise the largest barrier to transparency, the failure to publish, and the resultant bias in published information,” they write.

NCI Steps Up to the Plate
In a second commentary in The Oncologist, James Doroshow, M.D., director of the Division of Cancer Treatment and Diagnosis at NCI, said that he has no quibble with the data cited by Curt and Chabner. The failure to accrue patients and inefficiency in starting trials were documented in a series of published, NCI-supported studies by David Dilts, Ph.D., and Alan Sandler, M.D., both of Vanderbilt University. “And we are operating on that data to make improvements in the system.” Doroshow said. This includes methods to speed up the start of a clinical trial and to ease the paperwork that stymies industry–academia collaborations in clinical trials.

Two other changes are on tap that Doroshow believes will go a long way toward increasing the reporting of clinical trials results. One is that NCI will develop its own clinical trial database to capture all the administrative and outcome data for all clinical intervention studies that are performed at NCI-supported institutions. A pilot phase will be implemented in July 2009 that requires these institutions to report patient accrual information quarterly.

But the most far-reaching change, he said, is one that was signed into law in September 2007. President Bush approved the Food and Drug Administration Amendments Act (FDAAA) requiring that, starting September 2008, all phase II, III, and IV clinical trials registered in the clinicaltrials.gov database must report key results of the main outcomes no later than 12 months after data for the last subject were received. NCI’s own database will complement this effort, Doroshow said, by requiring that some outcome data be reported during the course of the 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,” Doroshow said.

Industry’s Role in Publication Woes?
An issue that was not explored in The Oncologist is the possible failure of the pharmaceutical industry to publish disappointing results. Ramsey had found that less than 6% of industry-sponsored studies have been published and 75% of those published studies had reached a positive conclusion.

Pharmaceutical companies, which now sponsor most cancer clinical trials, have
different motivations for publishing their results, Chabner said. “Academics see advancement in publishing studies. The most important thing for industry is doing the trial and seeing the results,” he said. “It isn’t so much about publishing because they are doing the trial for a purpose—to get a drug approved.”

But, he says, their editorial didn’t specifically address industry’s role in publishing cancer clinical trials because “it was easier for us to get the information about NCI trials.”

That is always the case, said Kay Dickersin, Ph.D., director of the center for clinical trials at the Johns Hopkins Bloomberg School of Public Health. “Their files aren’t open, so people don’t usually have any access to information that might explain why results from an industry-sponsored trial were never published or made available in another form.”

There are occasional exceptions, such as data that come out of court litigation or through submissions to the FDA, she says. And, in fact, a study published in the November issue of *PLoS Medicine* compared the information that companies share with the FDA about drugs with what they eventually publish. Researchers at the University of California, San Francisco, looked at data included in 164 trials for 33 new-drug applications approved by the FDA in 2001 and 2002 and found that by June 2007, one-quarter of trials went unpublished, and these were ones with predominantly negative results. The researchers also identified discrepancies between the primary outcome, statistical analyses, and conclusions presented in the drug applications compared with what was published.

As difficult as it is to address these issues, it must start with “people policing their own shops,” said Daniel Haller, M.D., editor in chief of the *Journal of Clinical Oncology*. Requiring researchers to publish outcomes in a national database may turn out to be overkill as well as difficult to enforce, but keeping tabs on one’s own research network is quite doable, he said.