JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 7, No. 7, July 2011 "Can You Handle the Truth?"

Study Registration Loopholes

By Carleton Southworth

Medical science is delayed when clinical studies and their results are hidden from public view. Traditionally, medical journals make information about clinical studies available to the public. Publication space is limited, however, so editors decline to publish articles on studies with faulty methodology, redundant or inconclusive findings, suspect validity, unknown authors, or simply poor writing.[1] Other studies are not submitted for publication (or buried in obscure journals) to serve the author's or funder's interests. For example, pharmaceutical and medical device companies are dismayed when studies they fund show negative results for their products, especially if they demonstrate inferiority to competing products.

Numerous studies have demonstrated a publication bias against such articles. For example, in one literature review, studies funded by pharmaceutical companies were found to be four times more likely than independent studies to give results favorable to the company. A sample of 56 studies comparing one painkiller to another all found that the sponsor's product was superior, i.e., A was superior to B, which was superior to C, which was superior to A.[2] Rowell and Burton report an instance where publication of negative findings relating to side effects was suppressed. Deferiphone was being studied to treat thalassemia (a disease that causes "iron loading" in the blood). The manufacturer, Apotex, funded the research. When evidence of diminished effectiveness over time and drug-induced liver damage was found, Apotex acted strongly to prevent distribution of this information, including suppression of publication.[3] Bekelman et al investigated 37 articles found on Medline that included quantitative data on financial relationships between industry, scientific investigators, and academic institutions. They found that industry sponsorship was associated with publication restrictions.[4]

The mechanisms behind bias are often unclear. Medical journal editors are motivated to publish high-impact articles that interest their readers. Investigators are motivated to publish articles that do not antagonize study sponsors. On the other hand, investigators qualified to receive funding and authorial support from pharmaceutical and medical device companies probably produce articles that are more publishable.

Other reasons why an article might not be published include the following:

- A parallel study of similar design but differing treatments yields results with greater impact.
- The topic is no longer popular, or numerous articles have recently been published in the same area.
- The author is discouraged because the article has been rejected by one or more journals.
- The results support a theory that the author, editor or reviewers dispute.[5]

Although a study may be inconclusive or redundant, publication is still important because the results can be combined with results from other studies in meta-analyses to yield definitive findings about the best treatments.

Addressing the Issue of Non-Publication

The issue of non-publication has been addressed in three major steps:

- The FDA Modernization Act of 1997 (FDAMA) authorized creation of "a registry [www.clinicaltrials.gov] of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act." (113(j)(3)(A))[6]
- In 2004, members of the International Committee of Medical Journal Editors (ICJME) agreed to limit publication of prospective clinical trial results to studies that have been registered in a public database.[7]
- The FDA Amendments Act of 2007 (FDAAA) requires publication in the www.clinicaltrials.gov registry of results and other information about each "controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act." (801(a)(j)(1)(A)(iii)(I))[8]

These rules have created a more transparent environment for clinical trials. However, they have not eliminated the motivations that create publication bias. We can therefore expect the publication bias effect to diminish but not disappear.

Studies Exempt from FDAMA and FDAAA

FDAMA and FDAAA only cover clinical studies with INDs and IDEs. Federal regulations (21 CFR 312.2((b) and 21 CFR 812.2(c)) provide IND and IDE exemptions for studies that meet various criteria like "the [drug] investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication." In other words, a sponsor might initiate a study without the intention to include its results in a New Drug Application (NDA), but later decide to include the study if the results are positive. However, the FDA probably would not consider it a "well-controlled" study for pivotal trial purposes. Nevertheless, thousands of investigator-initiated, post-marketing studies without INDs or IDEs are conducted every year to explore new indications, populations or dosing regimens. (Note that ICJME rules still apply to these studies.)

Studies Covered by FDAMA and FDAAA

Motivated study sponsors and investigators can find loopholes in FDAMA and FDAAA for drugs and devices intended to be covered by the laws, including the following hypothetical examples:

Example 1

An established pharmaceutical company, Company W, has just gained approval for a new drug, Drug A, to treat asthma. It has conclusive evidence from an active-control study that Drug A is superior to an older competing drug for treating Symptom 1. Drug A might also be superior for treating Symptom 2, but no studies have been conducted or required by the FDA for post-marketing follow-up.

Company W could conduct a clinical study of Drug A treatment of Symptom 2, but it would have to publish the results, even if negative. So, Company W instead initiates a small, registered study to further investigate treatment of Symptom 1, e.g., with a patient education component. The protocol also calls for collecting data on Symptom 2 as a low-profile, secondary endpoint but does not include a planned test for this symptom in the statistical analysis plan.

When the study is complete, Company W evaluates the impact on the secondary endpoints, including Symptom 2. If "serendipity" yields Symptom 2 results favorable to Drug A, the

investigator submits them to a journal. If the results are unfavorable, the statistical test results of Symptom 2 go unpublished.

This strategy limits the sponsor's risk of being forced to publish negative results. However, it might also create a study of inferior design. For example, in this hypothetical study, subjects were stratified by pre-treatment severity of Symptom A, not Symptom B. Because the severity of Symptom 1 and Symptom 2 are poorly correlated, the study population is unbalanced, and the power of the study is reduced. For definitive results, another study must be conducted, delaying widespread use of Drug A and imposing risk and inconvenience on a new set of study subjects.

Example 2

A medical device company, Company X, has developed and gained 510(k) approval for a new knee brace, Device B, aimed at maintaining kneecap stability. Company X wants to know whether Device B performs better than its predecessor model, thereby justifying a higher price.

Company X could conduct a clinical study comparing the two knee braces head to head, but it would have to publish the results, even if negative. So, Company X instead conducts two studies, pretending there is no connection between the two. Company X then combines the data from both studies, using covariate statistical analysis methods to account for differences in the two groups of study subjects. If the results are favorable, Company X submits them for publication. If not, Company X does not publish the results and leaves it to the marketing department to promote the new knee brace as best it can.

This strategy limits the sponsor's risk of being forced to publish negative results. However, it conducts studies of inferior, non-randomized designs. Alternatively, patient care could be compromised by randomizing between a knee brace and an untreated group in each of the two studies, even though an active control likely to be effective — the other knee brace — is available.

Example 3

A start-up, in-vitro diagnostic (IVD) company, Company Y, has developed its first product (Test C), a low-cost test for Hepatitis C. Company Y initiates a non-significant risk study using existing, anonymized blood specimens from individuals who do, or do not, have Hepatitis C. To maintain eligibility to publish in a prominent journal, Company Y registers the study.

Preliminary results are ambiguous. After an interim analysis, the test appears to be sensitive and specific in pediatric patients, but preliminary results also show that the few test failures observed occurred in adults. Therefore, Company Y becomes concerned that the study may not demonstrate the dominance of their technology predicted by their business plan. Citing limited financial resources, Company Y terminates the study early, thereby avoiding the publication of potentially definitive findings not in its favor. It then reformulates some inactive ingredients and now calls the product Test C+. Company Y then conducts a new study limited to pediatric patients, which yields positive results for children. They hope that, by inference, results may be taken by medical providers to suggest that Test C may also work well in adult patients. Company Y defers conducting a new study on specimens from adult patients until it determines how Test C+ performs in the market, including off-label use.

This strategy avoids the risk of publishing negative results. However, it delays the availability of Test C (now "reformulated" as Test C+) for adult patients, except in off-label, unproven use.

Example 4

Two collaborating academicians, Z_1 and Z_2, have identified a biologic agent, Biologic D, that shows promise for treating precancerous melanoma lesions in two animal models. Z_1 is based in the U.S. and Z_2 is based in a country that does not require clinical study registration. With financial support from a wealthy individual, they have conducted a Phase I trial that shows a good safety profile for Biologic D. They now want to proceed with a Phase II clinical trial.

Biologic D might become a blockbuster, so Z_1 and Z_2 do not want potential competition — academic or commercial — to know what they are doing. They therefore decide that study registration would reveal too much information. Accordingly, they conduct a Phase II study in Z_2's country, where registration is not required. The study shows positive results, but inadequate funding compromises the quality of the study. As a result, availability of Biologic D is delayed because a new Phase II study must be conducted.

Conclusion

As long as researchers have a vested interest in the outcome of the clinical studies they conduct, the temptation to game the system will exist. The purpose of this article is not to provide a roadmap for circumventing FDAMA and FDAAA. Rather, it is to alert people to the loopholes so any actual instances can be recognized and prevented on ethical grounds.

Researchers should conduct studies that are optimized to demonstrate an experimental therapy's safety and efficacy, without consideration of registration issues. Any discussion of registration in connection with study design is a bright red flag.

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Acknowledgement

The author would like to thank Elisabeth Southworth for editorial assistance.

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