Clinical Trial Registration, a Needed Addition to the Research Process

During the past few months, I have been reading a series of articles published in the Philadelphia Inquirer. These articles have been interesting but also very disturbing.

A local teenager committed suicide shortly after initiating antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) to treat her for severe depression. Members of the US Food and Drug Administration (FDA) Psychopharmacological Drugs Advisory Committee and Pediatric Committee of the Anti-Infective Drugs Advisory Committee reviewed over 400 case reports of pediatric patients receiving SSRIs who attempted to harm themselves or who at least had suicidal ideation. Concern for an adverse association might exist, and congressional investigations are underway as to the FDA’s failure to protect the public health and its suppression of evidence related to these adverse events. On February 22, the FDA requested 10 pharmaceutical manufacturers of brand-name SSRIs update their labeling to warn of the possible risk of suicide in both minors and adults who initiate this form of therapy.

When this issue of potential risk first came to the public’s attention, pharmaceutical manufacturers stated that suicide and suicidal thoughts were not identified during the clinical trials that were conducted before the release of SSRIs. The FDA claimed that well-controlled, published clinical trials showed that these medications were safe and effective. However, plaintiff lawyers and knowledgeable clinical investigators had claimed that all the data generated by clinical trials focusing on these medications were not published and, in fact, the potential for these adverse events could have been identified if all the data had been available for review by clinician researchers.

I would like to tell you a relevant incident of which I have first-hand knowledge. When I was a young faculty member, I was involved in trial for an inhaled respiratory medication. A variety of published European studies had clearly demonstrated the efficacy of this medication. Clinical trials were then started in the United States to gain FDA approval.

Our study, which involved a relatively small number of patients, clearly demonstrated that this inhalative increased cardiovascular risk. Yes, it had an impressive degree of efficacy, but my co-investigators and I were concerned about the cardiovascular changes we identified when this medication was used on a regular basis.

Fortunately, the medication was being tested in young patients, a population that could well tolerate the principal adverse effects. It was clear to our team of investigators, however, that if the medication were used in older patients, particularly those with underlying cardiac disease, the medication could be harmful.

We reported our data to the sponsoring pharmaceutical company, which had substantial concerns but also a degree of reluctance to believe our results. This reluctance was unfortunate, because the study was a well-designed, placebo-controlled clinical trial. In addition, we were confident that a research bias was not the cause of the cardiovascular change that we were witnessing. When the study became unblinded, it was clear that this cardiovascular adverse effect was associated with the medication that was being tested, as the adverse effect was not found in the patient group that received placebo.

We eventually reported our results in abstract form at a national medical meeting, but the sponsoring pharmaceutical company substantially resisted our request to submit the data to a peer-reviewed medical journal in full manuscript form. To make a long story short, this medication never made it to the US market and was eventually withdrawn. However, our’s was not the only study that identified the drug’s substantial cardiovascular risk and its associated increased morbidity and eventually recognized risk for mortality. An eventual investigation by regulatory agencies identified causality, and the medication was banned worldwide.

I learned a lot from the inhalative medication clinical trial, so it should come as no surprise that I am strongly in favor of clinical trial registration.

In September, the International Committee of Medical Journal Editors (ICMJE) issued a statement supporting a clinical trial registration process that will substantially change the way in which clinical trials will qualify to be published in the peer-reviewed medical literature in the future. As a condition of consideration for publication, the 11 journals whose head editors belong to the ICMJE will require that clinical studies involving human subjects be registered in public registries. In addition, the ICMJE editors have stated that all clinical trials must register before the onset of patient enrollment.

At this time, these editors do not advocate one particular registry site, but each journal will require authors of submitted manuscripts to have registered their trials at a registry that meet certain criteria. The registry criteria being considered at this time include easy public accessibility at no charge, openness to all prospective registrants, and management by a nonprofit organization. Furthermore, the site must ensure the
validity of the registered data and be easily electronically searchable. The editors suggested that the public registry be part of an existing site sponsored by the federal government (www.clinicaltrials.gov), which is hosted by the US National Library of Medicine.

The stand taken by the ICMJE editors is likely to have a huge impact on the pharmaceutical industry throughout the world. Every clinical trial involving humans will be expected to have been registered at an electronic site if the trial’s results are submitted for publication in any of the ICMJE 11 member journals.

I believe that this process must be extended beyond pharmaceutical trials and beyond ICMJE member journals. It should include any clinical trial that could be used to influence the thinking of patients, researchers, clinicians, and other experts who take care of patients, write clinical care guidelines, or even decide on insurance-coverage policy. To enforce this new process, the JAOA and other fine medical journals that have not been invited to be a ICMJE member will need to adopt the same policy.

This process will allow the many individuals who have a vested interest in clinical research to explore all the clinical evidence involved in a particular intervention, not just positive studies with favorable outcomes that are published in the literature.

Several drug companies have already started or are about to start posting information about their clinical trials on their company Web sites. Drug manufacturers can also post findings, both positive and negative, of their clinical trials on the publicly accessible Web site started by their industry’s trade association, the Pharmaceutical Research and Manufacturers of America (PhRMA). The PhRMA database, available at www.clinicalstudyresults.org as of October 1, includes both published articles and unpublished study summaries.

When I first found out about the ICMJE policy, I thought that it was directed at the pharmaceutical industry, but after careful consideration, I find that it involves all forms of clinical investigation involving human subjects, including nonpharmaceutical research such as osteopathic manipulative treatment. Although the JAOA publishes few pharmaceutical studies, it certainly publishes numerous studies on nonpharmaceutical clinical issues related to osteopathic medicine. I believe that it is important for the JOURNAL, the osteopathic medical profession’s leading peer-reviewed and indexed publication, to participate in this process. So like the ICMJE member editors, I intend to insist that all human trials submitted to the JAOA be listed pending the availability of a public registry and further discussion by the profession.

Registration of clinical trials and the need for a comprehensive tracking system for the reporting of results of all these trials is long overdue. It is time that physicians and the public have access to the results of all trials, not just trials that have favorable results. An expanded body of knowledge that is easily available and accessible can only enhance the clinical research process. I strongly believe that required trial registration will advance the science of osteopathic medicine.

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Addendum—Late breaking news!
Just as this issue of the JAOA is going to press, word comes that on October 7—just shortly before Congress adjourns—Democratic lawmakers introduced federal legislation that would require pharmaceutical and medical device manufacturers to register clinical trials of their products when they begin their trials involving patients at an academic institution or a private clinic. It would also require these manufacturers to report results on a public database. Action on the bill is not likely to occur until after the presidential election on November 2.