

Point-Counterpoint: ClinicalTrials.gov: Bureaucratic Nuisance or Opportunity to Improve the Field?

In a prior issue of the APOR newsletter, Satish Raj wrote an opinion piece suggesting that the application of the current ClinicalTrials.gov requirements was unduly burdensome to small Patient-Oriented Investigators. Although he fully supported the intent of ClinicalTrials.gov (to prevent the “burial” of industry sponsored clinical trials with results unfavorable to the sponsor), his concerns dealt with the “paperwork” burden applied to both a large 10,000 subject industry sponsored randomized trial and to a small investigator initiated 10 subject trial. Further, because many of these small patient-oriented studies are focused on discovery (“first in man”, “first in disease”) and assessing physiological responses and not on providing definitive answers to a question for which there is a solid foundation of human experience, the ClinicalTrials.gov website seemed designed for the latter type of research. Therefore, the goal of the Raj “Opinion” piece was not to argue for unregulated research, but rather to point out that there are different types of research, and that there could be recognition of this with a more nuanced reporting regulation based on the nature of the research (discovery vs. definitive answer to a clinical question) and size of the projects. This approach is used elsewhere in the FDA. In the following, Dr. Robert Califf, a pre-eminent clinical trialist, and Dr. Deborah Zorin, Director of ClinicalTrials.gov, provide an alternative perspective.

We have read with interest the impassioned expression of concern by Dr. Satish R. Raj, published in the December 2009 APOR Newsletter [1], regarding the expansion of regulatory burdens imposed by the ClinicalTrials.gov registry. In his editorial, Dr. Raj raises a number of issues relating to changes in reporting requirements, particularly mandated reporting of trial results and the expansion of the registry to include earlier-phase research—developments that Dr. Raj characterizes as likely to lead to undesirable, albeit unintended, consequences. Specifically, Dr. Raj posits that these expanded reporting requirements will impose excessive and costly administrative burdens on investigators, especially academic investigators working on early-phase research or discovery science; may result in a glut of confusing information for patients and healthcare consumers; and may simply be inappropriate for some kinds of research activities.

We also are concerned that translational investigators working at the interface of laboratory research and human studies face a period of great challenges and significant hurdles. However, we firmly believe that the ClinicalTrials.gov registry, rather than constituting a pointless, bureaucratic burden, offers significant opportunity for investigators engaging in patient-oriented research (POR). We hope that as more POR investigators turn to ClinicalTrials.gov, the benefits afforded by a complete, easily accessible record of human experiments and their corresponding results will spur significant improvements in the field. Although we believe that ClinicalTrials.gov will enable investigators to improve their methods while accelerating the growth of knowledge about human biology, several key points raised by Dr. Raj deserve a direct response in the interest of providing a different perspective.

The History of ClinicalTrials.gov

The ClinicalTrials.gov registry has its origins in the Food and Drug Administration Modernization Act of 1997 (FDAMA) [2], and was intended to help persons with serious or life-threatening diseases find clinical studies in which they might want to participate. Once the database was constructed, federal law and other policy requirements expanded in response to societal concerns about research, including not only the negative reporting bias that Dr. Raj discusses, but also human subjects protections, scientific integrity, support for evidence-based medicine, and allocation of research resources. Well-publicized failures of integrity with regard to both fundamental ethics and scientific principles have further amplified these concerns and increased demands for greater transparency and accountability.

Contemporary clinical research proceeds according to the following basic process: 1) institutional review boards (IRBs) assess studies to determine whether they offer an acceptable balance of risks and benefits; 2) human volunteers participate in research after being informed of these potential risks and benefits, and after being assured that by participating, they will contribute to generalizable medical knowledge; 3) clinicians and patients use the resulting data to guide their medical decisions; and 4) institutions that fund research make decisions, informed by the results of these studies, about the allocation of precious resources for new research.

Each of these steps requires confidence that all data relevant to making informed decisions are available for consideration. In addition to concerns about access to data, shortcomings in the integrity of the design, conduct, and analysis of research studies further undermines trust in the entire enterprise. For this

reason, full transparency, achieved through public reporting, is a crucial first step in ensuring the scientific and ethical integrity of human subjects research and is essential to maintaining public confidence in clinical research. It is difficult for us to understand how these points are not applicable to the types of biological studies done by POR investigators.

What Is Required?

Current U.S. law under the Food and Drug Administration Amendment Act of 2007 (FDAAA) [3] mandates the registration of certain Phase II-IV drug and device trials and requires the reporting of summary results for some of these studies. The law does not demand reporting of Phase I studies. The International Committee of Medical Journal Editors (ICMJE) [4], on the other hand, requires registration of all interventional studies of human subjects, regardless of phase, intervention type, or geographical location, prior to the enrollment of the first study participant; the ICMJE does not mandate results reporting, and allows registration in either ClinicalTrials.gov or one of several other registries approved by the World Health Organization (WHO). While this requirement has no legal force, it is a prerequisite for publication in many biomedical journals [5]. For these reasons, any investigator in the U.S. or who is subject to FDAAA would be wise to register all interventional human studies in ClinicalTrials.gov, and, at a minimum, to report results for those required under the FDAAA.

Academia and Publishing

In his remarks, Dr. Raj advances the commonly held belief that publication bias is an industry problem and that academic research is always published. Unfortunately, the data do not support this contention. For example, Bourgeois and colleagues reported that only 55% of a sample of non-industry drug trials in ClinicalTrials.gov had been published within 2 years [6] and Ross et al. reported that 47% of government-funded studies were published [7].

Burdens Associated with the Results Database

Although some believe that the ClinicalTrials.gov results database is overly burdensome, it consists of tabulated data that would have to be made available at the end of any study (and would certainly be required for publication). These data include such items as study participant flow (how many people started and completed each arm), baseline characteristics (age and sex, at minimum), summary statistics for each prespecified outcome measure (e.g., mean and standard deviation), and adverse events. It is simply not credible that a responsible investigator would not ensure ready access to such data at the end of a study.

Discovery vs. Confirmatory Research and a priori Endpoints

Dr. Raj posits that POR as an enterprise is characterized by a more open nature than confirmatory research, which has a definite structure and begins with a hypothesis that can be confirmed or rejected. Several issues deserve mention here. First, we believe that POR, like all scientific experimentation, should start with a clear hypothesis along with a prespecified set of actions that will permit the hypothesis to be accepted or rejected. Second, the statistical basis for drawing a conclusion from research requires a structure in which a question is asked, an analysis is done, and the probabilities that the answer is consistent with the hypothesis (or that the answer excludes the possibility of a counterhypothesis) is quantified.

While the underlying framework may be frequentist or Bayesian, we cannot escape the need for a probabilistic approach to analysis, which should be specified before the study is initiated. Although we agree that outcomes that were not prespecified may lead to critical scientific discoveries (or hypotheses), it is worth noting that these are not covered by mandatory reporting requirements. Further, regardless of whether the research is patient-oriented or pragmatic, an observation should be considered preliminary until it is confirmed by subsequent studies. We prefer the terms “explanatory” or “mechanistic” to denote the type of research described by Dr. Raj, as opposed to “pragmatic” trials primarily intended to guide medical decision-making, but we do not see any reason for the degree of transparency or methodological rigor to vary, regardless of the type of research.

Too Much Information Is Confusing

We must admit to finding Dr. Raj’s contention that the information afforded by ClinicalTrials.gov constitutes a potentially confusing excess to be especially problematic. While it is true that wrong conclusions can be drawn from accurately reported data, it is also true that throughout history and in multiple disciplines, transparency of action has led to the greatest overall good and has helped rather than hindered the progress of research. Whether a study is pragmatic or mechanistic, we ask human volunteers to sign a consent in which we promise to create generalizable knowledge with the trial results. It is difficult to argue that we honor that promise by keeping the study design and results secret. The concept of “secret human experimentation” does not pass the “sniff test”—indeed, it runs counter to the entire current of modern bioethics.

Unfunded Mandates

We find Dr. Raj’s comment that academic studies should be exempted from registration requirements because of the effort needed to register and report the results of human experiments to

be particularly concerning. We acknowledge that this may raise legitimate issues for the individual investigator, but his argument about the greater capacity of industry to do this seems specious. The majority of POR done is done at major academic medical centers (or academic health and science systems [AHASs]). Most of these AHASs have hundreds of investigators and protocols, and revenues exceeding \$1B when the academic and health delivery systems are considered in combination. There is no fundamental reason why such major entities could not assist their investigators by supporting the necessary infrastructure. For example, the National Institutes of Health (NIH) is currently supporting efforts to centralize and support these activities through the Clinical and Translational Science Awards (CTSAs).

References:

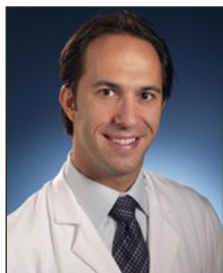
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Conclusions

ClinicalTrials.gov has evolved through a complex but public debate about the obligations of those who perform experiments on human beings. While investigators who do Phase I studies are not required to register their studies or their results, we hope that the POR community will embrace the spirit of transparency by voluntarily entering their studies with ClinicalTrials.gov. In doing so, they will help improve this important tool and, in turn, further accelerate the advance of scientific methods and knowledge.

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Junior Investigator Spotlight: Jeffrey S. Berger, MD



Jeffrey S. Berger, MD

Despite great advances in the prevention, diagnosis, and treatment, cardiovascular disease remains the number one cause of death in the Western World. To help combat this major epidemic, much of my work focuses on measuring platelet activity to better understand the role of platelets in the initiation and progression of atherothrombosis. I believe that combining

markers with different pathophysiological mechanisms of platelet activity offers the opportunity to better understand if one or any combination of platelet markers is independently associated with the incidence and progression of cardiovascular disease.

I am fortunate to have several funding mechanisms to help me approach this area of research, both in the basic science and clinical research arenas. As a Cardiology Fellow at Duke University and the Duke Clinical Research Institute, I was awarded an American Heart Association Fellow to Faculty Award to study the relationship between gender, platelet activity, and platelet directed therapies. Using this grant as a platform and after additional training at the University of Pennsylvania in Vascular Medicine and Thrombosis and Hemostasis, I made the

transition to a faculty position at New York University School of Medicine as an Assistant Professor of Medicine and Surgery in the Divisions of Cardiology, Hematology, and Vascular Surgery. During my first year as a faculty member, I started a platelet laboratory program measuring a panel of different platelet function assays, supported by several grants awarded from the CTSI at New York University. Building on this foundation, I recently applied and was awarded a Doris Duke Charitable Foundation's Clinical Scientist Development Award for a study on platelet activity in cardiovascular disease.

Much of my early success is derived from a strong foundation in training in clinical research through the K-30 sponsored masters program at Albert Einstein College of Medicine. Additionally, my passion and drive are very strong to help find innovative ways to better understand both the pathophysiology of cardiovascular disease as well as markers that will aid in the diagnosis, prognostication, and treatment of cardiovascular disease. I am excited to wake up every day and face the challenges that present. I hope that with continued collaborations and wonderful mentorship, I will have the opportunity to make advances in the field of cardiovascular diseases.