Commentaries

A New Paradigm for Clinical Studies?

Most readers are not clinical trialists but we are all affected by the results of clinical trials and are therefore interested parties in their design and logistics. Performing clinical trials is not easy, but how hard depends on where you are in the hierarchy. The foundation of any trial is, of course, an idea. Some are clever and reveal creativity and a deep understanding of a problem, but these are few and most are pretty straightforward, requiring little imaginative thought. For example, why not determine if drug X cures problem Y in a particular disease? A drug that works on one autoimmune disorder might work on another. Yet some drugs are not tested for obvious indications, and may be used liberally although there is no data to support its use. “It makes sense that if it works in population A it will work in population B” but only if A’s ailments share some pathophysiologic substrate with B’s problems.

In my niche, I regret to report that there have been no studies on the treatment of anxiety in Parkinson’s disease (PD) although anxiety affects 25-40% of people with the illness and there is reason to question whether drugs that work in the general population will work in PD, which likely has a different pathophysiology. The reason for this lack of data is funding.

How do trials get funded? Most are sponsored by pharmaceutical companies that have a product to sell. This means we don’t try to find out which is the “best” drug for treating a PD-related problem, only whether drug X produces significant benefit and is tolerated. Sometimes someone gets an idea to test a drug for a new indication. When the drug is under patent, the company may sponsor such a trial, partly to increase the drug’s exposure, and partly to enhance the drug’s reputation, possibly even to have its benefits extended into “off label” uses, as was the case for gabapentin that sold more for off-label use than on. However, when a drug is not under patent, the potential funding is much harder to get. There are foundations which may sponsor treatment trials, but trials are enormously expensive, and the NIH is therefore left to sponsor most trials, usually at great expense. The foundations can’t afford to fund many trials and tend to focus on basic research, which is where the cures or the preventions are going to be found, and which are much less expensive and faster at producing results.

To apply for an industry grant requires only a little effort and has a high rate of return. Since the usual applicants for grants are experts in the field who have clinical trial experience, it usually takes only a few-tens of hours to put together a protocol and a budget, and the company usually responds fairly quickly, taking weeks to months. The NIH is a very different story, with grant applications taking hundreds of hours, often with many busy individuals involved, and no room for error or flexibility. The rate of return is miniscule. The rate of grants being funded varies with the Institute, but a figure as low as 3% is one that was quoted to me recently. This means that only the top 3% of applicants were funded. This is 3% of applications written by university professors with lots of experience, publications and established records. Most institutes fund a higher percentage, probably about 10%. This means that several people will spend hundreds of hours to no purpose. This translates into many people not bothering to “waste” their time by writing grants unlikely to be funded, regardless of their quality. Since the decisions to fund are based on multitudinous considerations, including how “important” or “novel” or “sexy” the proposal, non-sexy, non-novel, non-life-changing treatment trials may not be funded. Which brings us back to anxiety in PD, or apathy in PD or fatigue in PD.

My suggestion is only partly novel. I propose that funding institutes define clinically important problems and instead of putting out an “RFP” (request for proposals), put out a request for interested parties. From this group of interested parties, a handful of experts would be chosen to design a clinical trial and then choose the sites from the other interested applicants. The National Institute of Neurological Disease and Stroke currently has a project testing medications that might be protective for PD patients, that is, might slow disease progression. Estimating that only drugs with significant benefit are worth testing, only small numbers of subjects are required, and multiple drugs can be tested over relatively short periods of time. But there is no reason this concept cannot be extended to other treatments in every disease that has unmet needs, which is probably most diseases.

This approach to disease treatment is only partly competitive, in that interested parties would compete for participation, which will undoubtedly lead to the more famous, better established having a clear advantage over other interested parties. But to think that this is not already the case in the review process would be naïve. Certainly a clever idea might emerge in responses to RFP’s that might not in a setting where the participants were chosen by their interest and track record. However, one can easily imagine a process in which, in addition to public solicitations for interested investigators, requests for ideas to study and skeletal outlines for proposals are made, and, judging by the responses, certain potential investigators could be invited to flesh out their proposals and possibly present them before review panels.

Our current approach may be the most efficient long-term, when money is available, but is undoubtedly not efficient when money is tight, since most potential investigators, perhaps those with the best ideas, choose not to participate because of the low yield.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers’ Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001–2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.