

The Era of Clinical Trial Registries

A WHITE PAPER

INTRODUCTION

The pharmaceutical industry finds itself plagued by drug safety concerns and scandal as prescription drugs continue to make headline news around the world. Currently, the general public has a high level of distrust regarding pharma companies. This lack of trust is largely based on the limited availability of timely information regarding the clinical development process. The steady drop in clinical trial enrollment by patients is also a likely reflection of this general lack of faith. The bottom line is that healthcare professionals and consumers are demanding broader access to trial results—both positive and negative.

Many healthcare professionals and patients are frustrated by the lack of access to comprehensive information about clinical trials and their results. Increasing demand for more balanced and timely information on prescription products has spurred the creation of clinical trial registries.

Fundamentally, people want to know that they have access to *all* the information regarding trial results. It is for this reason that many government agencies, industry associations, and pharma companies have launched clinical trial registries and databases over the past few months.

The objective of clinical trial registries is to make information about clinical trials available to both healthcare professionals and the public in an unbiased, scientific, and timely manner. In other words, registries do not offer interpretations or conclusions. The results of the clinical trials—positive or negative—are published in full.

This provides much greater transparency of treatments in the clinical trial process, as well as products in post-marketing surveillance studies. It is believed this transparency will enhance patient care by providing physicians with objective and comprehensive data on all products, including those under development.

The increased availability of information creates the desired transparency, but at a price. Pharma companies must bear registry setup and maintenance costs while finding a way to manage the potential avalanche of questions from healthcare professionals and consumers.

Beyond these more direct expenses, there are also financial implications of making proprietary knowledge available to competitors. Without putting safeguards in place to protect intellectual property, the competitive advantage that ultimately drives drug sales could be eliminated. Widespread implementation of clinical trial registries and databases may ultimately reduce the incentive for companies to develop new drugs. A balance must be struck between addressing the public's concerns and encouraging the development of new products.

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BACKGROUND

One of the first initiatives in the transition to clinical trial registries was Section 113 of the Food and Drug Administration Modernization Act (FDAMA) of 1997. Section 113 established the National Library of Medicine's registry (www.clinicaltrials.gov) by requiring registration of all clinical studies for serious or life-threatening diseases or conditions, within 21 days of study inception. This system, first made available to the public in February 2000, was designed to make consumers more aware of clinical trials in which they could participate.

However, the legislation has had further-reaching consequences. Section 113 served as the platform upon which many groups have built their position on clinical trial registries. Organizations, such as the American Medical Association (AMA) and the International Committee of Medical Journal Editors (ICMJE), have called for a single trial registry. At the same time, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and other international groups have begun advocating specific principles for disclosing trial results.

In 2002, member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) pledged to provide the results of all hypothesis-testing studies. Hypothesis testing may occur at any stage of drug development and includes all phase 3 studies, some earlier-phase studies, and many studies of marketed products. PhRMA's pledge specifically excluded exploratory trials, unless the results were found to be of medical significance. This limitation was based on the proprietary nature of exploratory studies. The research that a pharma company chooses to pursue literally defines their business strategy. Clinical evaluations reveal a company's research agenda very early in the process by outlining the trial design and detailing expected endpoint measures.

PhRMA formally launched a clinical trial database in October 2004 at www.clinicalstudyresults.org. The site is a centralized repository for voluntarily disclosing study results for those products marketed in the US. PhRMA also issued a joint industry policy regarding voluntary disclosure and urged all companies to post unpublished trial results within twelve months of trial completion.

The AMA also became involved in the registries issue in late 2004. They outlined five key elements for clinical trials registries.

1. Include all phase 2 to 4 trials
2. Name the study sponsor, unique identifier, funding entity, and contact information for the key individuals conducting the study

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3. Specify information on the name, purpose and design of the study, disease(s), and population being studied, key study dates, location, and patient recruitment status
4. Contain results in a central repository, including links to sites containing additional published reports
5. Allow participation to be considered a condition for approval by Institutional Review Boards (IRBs).

In recent months, pharma companies have agreed to voluntarily expand upon the FDAMA Section 113 requirement to include **all** hypothesis-testing (i.e., mid-to late-stage) clinical studies - not just those for serious or life-threatening illnesses. By July 1, 2005, pharma companies will voluntarily post details on all newly-initiated hypothesis-testing clinical trials at study initiation, either on their respective corporate Web sites, at www.clinicaltrials.gov, or at www.clinicalstudyresults.org. All ongoing hypothesis-testing trials are to be posted by September 13, 2005. These postings must meet minimum standards, including

- Study description in easily understood terminology
- Study purpose, type, and phase
- Study status
- Type of intervention
- Illness or condition studied
- Inclusion/exclusion criteria
- Site location and/or contact information

Beyond these minimum requirements, some basic principles for registries were also agreed upon.

- Information on studies conducted outside of the US should be provided
- Standards for verifying adherence to these guidelines should be established
- Unique identifiers should be created for all trials listed on clinicaltrials.gov
- Complete protocols should be placed with a secure third-party for later disclosure

In addition to government and industry-wide policies, many companies have unveiled more detailed plans, specific to their respective companies, to increase the amount of clinical trial information available publicly. With the possibility of regulatory mandates lurking, certain industry players are attempting to set acceptable standards. GSK, Lilly, AstraZeneca, and other companies have already begun to post clinical trial results on their own corporate Web sites, generally following the basic formula laid out in the International Conference on Harmonization (ICH3) guidelines. Others (e.g., Roche) have announced plans to do so during the first half of 2005. Merck and other companies have committed to posting information on all hypothesis-testing phase 3 and 4 trials directly on www.clinicaltrials.gov, rather than on their corporate Web site.

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Limitations to publication eligibility laid out by the ICMJE are also encouraging companies to register this information. At a minimum, phase 2 to 4 clinical trials must register the following information:

- Unique identifier
- Interventions and comparisons being studied
- Eligibility criteria
- Number of patients
- Primary investigator's contact information
- Trial purpose (hypothesis)
- Primary and secondary endpoints
- Source of the funding for the study
- Key dates for the study

In order to comply with the ICMJE guidelines, trials starting after July 1, 2005, must be registered prior to or at the beginning of patient enrollment. For trials that are currently underway or are starting prior to July 1, 2005, registration is required by September 13, 2005. These dates are consistent with the joint industry position issued in January.

DISCUSSION

Several legitimate concerns are being raised by pharma companies regarding some of the proposed clinical trial registry requirements and expansions. One of the key purposes of clinical trials is to evaluate potential products for their effectiveness in treating specific disease states, in hopes of gaining regulatory approval. Maintaining confidentiality of this proprietary information at early stages is critical. Pharma companies' revenues depend on beating competitors to market with new or improved products. If companies are forced to share proprietary information early in the clinical trial process, they could lose significant competitive advantage. Substantial loss of the financial benefits of innovation could, in turn, deter pharma companies from investing as heavily in drug development.

New requirements also mean new expenditures. Costs associated with implementation, maintenance, and managing public feedback could be staggering; however, managing public opinion is increasingly important to pharma companies. After all, it is the public who ultimately purchase their products.

The idea behind trial registries is to allow the public and healthcare professionals to draw their own conclusions by publishing data without synopses or interpretations. While this may reduce bias based from the slant of the reported results, publication of uninterpreted scientific data opens a large window for misinterpretation. How will the public interpret results from similar trials with different outcomes? Without conclusions, how will consumers determine clinically and statistically significant results? How will the average person even understand this data?

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While the issue of preventing misinterpretation remains largely unanswered, the pharma industry has offered several suggestions for effectively maintaining corporate confidentiality without cost to consumer interests. The majority of these suggestions involve limiting the information published at trial initiation regarding clinical trial design. This would mean delaying the posting of certain pieces of information until the company can reasonably file for intellectual property protection or publish an article in a refereed journal.

In this scenario, the company's need to protect proprietary information could easily be balanced with the public's desire for disclosure. Companies could be required to publicly register an outline or overview to be updated as the trial progresses. In coordination with this effort, the complete protocol could be filed with an uninterested third party. This third party would maintain confidentiality until the study is completed or terminated. Because the clinical trial endpoints are defined upfront in the protocol, companies could not selectively disclose trial results. Therefore the public gets access to the desired information while the companies maintain the necessary level of confidentiality.

This solution maintains the original intent of trial registries—sharing meaningful trial information with the public. The desired transparency is created but at a time that would allow proprietary information to remain just that. This protection is critical to ensure the continued investment of billions of dollars in research and development by the pharma industry.

CONCLUSION

Clinical trial registries can offer significant benefits to consumers, healthcare professionals, and the pharma industry. However, registries must be set up effectively to realize these benefits.

From the view of pharma companies, a trial registry can be used by investigators to facilitate patient enrollment in clinical trials. The increased availability of information allows patients to identify trials they are interested in, assess safety and efficacy issues, and easily register to participate.

Registries also offer implied benefits, such as a potential reduction in the negative news coverage that currently undermines consumers' faith in the clinical trial process. Patients can use the information contained in the registry to track a particular clinical study and identify issues for discussion with their physician. The availability of such a tool for proactive consumer involvement could easily boost confidence and ultimately result in greater profits for the pharma industry.

With all these potential benefits and more regulations slated to go into effect, there is little doubt that the registry issue will remain front and center in 2005. As with any new

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endeavor, companies must proceed within well-defined parameters to define what will fit best with their overall business objectives. Creating a more comprehensive registry should result in increased public trust, greater clinical trial participation, and enhanced consumer welfare.

ABOUT CAMPBELL ALLIANCE

Campbell Alliance (www.campbellalliance.com) is the leading management consulting firm specializing in the pharmaceutical and biotechnology industries.

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