In Search of “Clinical Trial Register Version 2.0”

Imagine a website key word search that results in a comprehensive, up-to-date listing of concluded clinical trials from around the world.

Consider the knowledge to be gained from that website’s analysis function as it generates a comparison of valid, parallel data from the trials that peaked your interest. Picture the convenience of having the comparison in an easy-to-understand table that can be printed, emailed or saved to your computer.

Think of the advantages of 24/7 access to clinically relevant patient treatment information that is timely, credible, and strongly related to trial data. Envision the possible contributions not only to your work but also to evidence-based medicine.

This clinical trial register model holds enormous promise for researchers; funders; trial sponsors; patient advocacy groups; regulatory agencies; ethical review bodies; and practicing physicians and their patients.

Now, how would you like to access this register in the not-too-distant future?

Over the past decade, much has been written about the need for this type of clinical register. Regulatory rulings and laws have spurred a growing number of web-based registers. Unfortunately no single register fulfills the vision for a single-source repository of parallel data using uniform standards and a layered search function to provide user data mining, comparison and analysis.

The time is right to take the best of what currently exists and focus its content and functionality on real-world user wants and needs. An appropriate metaphor for realizing this vision is the product enhancement of computer software. After product introduction in the marketplace, software designers, expert users, and early adopters collaborate to review the product’s original concept to add or refine user benefits and functionality. The updated product is denoted “Version 2.0.”

Since the launch of the clinical trial register concept sufficient time has elapsed for developer organizations and stakeholder groups to reflect on and discuss the best of what exists and the potential of what could be. It is time for collaboration as we search for “Clinical Trial Register Version 2.0.”

The Clinical Difference between Register and Registry

Medical science media often use the words “register” and “registry” interchangeably. *Ongoing* clinical trials are aggregated in a registry. Clinical trial *results*, the focus of this chapter, are aggregated in a clinical trial register.

The term ‘clinical trial’ has been defined in numerous references with perhaps the most comprehensive one being crafted by members of the International Committee of Medical Journal Editors (ICMJE) in a 2004 editorial **(**1**)** and subsequently updated in 2005. **(**2**)**

> *“Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. A trial must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration.”*

The ICMJE describes “medical intervention” as meaning any intervention used to modify a health outcome. It further defines it to include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, etc. **(**2**)**

The Case for Registering Concluded Trials

Clinical trials can be sponsored publicly or privately. Their data and findings are invaluable to medical science and form the basis for evidence-based medicine. Yet many concluded trials are never reported by sponsors. As a result, their findings cannot contribute to the evidence base for healthcare decision making. Their absence widens the knowledge gap in medical research and funding, and may result in duplication of effort and wasted resources. The ultimate price associated with unreported clinical trial conclusions can occur when negative findings result in the loss of human life.

There are a multitude of reasons why a sponsoring organization does not report clinical trial findings. The most widely cited is the intense competitive environment surrounding

many private company sponsors. Concerns such as these are legitimate and deserve serious consideration.

Increasing Stakeholder and Government Interest

The topic of aggregating clinical trial facts and findings into a central repository was first discussed within the medical science community in 1986. **(**3**)** The web-based concept was to be a resource through which clinical trials would be included in a comprehensive, searchable database. Since then not only has the medical science community embraced the concept, but also patient advocacy groups, regulatory agencies and, as a direct result, legislative bodies including the U.S. Congress.

The need to balance the interests of patient advocates, private clinical trial sponsors, research funders and other groups have resulted in two pieces of legislation currently before the U.S. Congress. As of February 2006 the Fair Access to Clinical Trials Act and the Clinical Research Act are in committee. Both Acts promote the use of public registers and/or registries.

The Fair Access to Clinical Trials Act (S.470 and H.R.3196, and introduced as H.R. 5252 in the prior Congress) amends the Public Health Service Act to expand the scope of information required for the data bank on clinical trials of drugs, and for other purposes. It requires that a clinical trial be registered before its commencement, stipulates the trial facts that must be publicly disclosed in a manner that is “readily accessed and easily understood by members of the general population.”

The Clinical Research Act of 2005(S. 1543 and H.R. 2308) provides for clinical research support grants, clinical research infrastructure grants, and a demonstration program on partnerships in clinical research, and for other purposes. One of the Act’s requirements is that the Director of the National Institutes of Health (NIH) is to award clinical investigator advancement grants to eligible academic health centers to support the translation of basic science to patient care by implementing and conducting all aspects of their clinical research mission. In addition, it also requires the Director to award clinical research infrastructure grants to eligible academic health centers to foster the use of information technology to facilitate the transformation of basic

research findings on disease mechanisms into the development of new methodologies for diagnosis, therapy, and prevention.

Increasing government interest in promoting trial data information that has the potential to benefit patient treatment has created the initial impetus for repository development and the growth of *both* registers and registries. While a large number of clinical trials are conducted by pharmaceutical companies, not all provide their results on their company websites, but rather publish them on ClinicalTrials.gov or ClinicalStudyResults.org. Table 1 provides a list of major pharmaceutical companies that publish proprietary clinical trial registers.

TABLE 1. U.S. PHARMACEUTICAL COMPANY CLINICAL TRIAL REGISTERS

Company	Clinical Trial Register URL
Bayer Healthcare	http://www.bayerhealthcare.com/index.php?id=222&L=2
Eli Lilly and Company	http://www.lillytrials.com/
GlaxoSmithKline	http://ctr.gsk.co.uk/welcome.asp
Hoffman La Roche	http://www.roche-trials.com/

Highlights of key websites that aggregate clinical trial data include:

- ClinicalStudyResults.org

  Government interest on behalf of patients and clinicians encouraged pharmaceutical companies to make concluded clinical trial data available to the public. Collectively, through The Pharmaceutical Research and Manufacturers of America (PhRMA) they created a central, web-based repository for clinical study results in a reader-friendly, standardized format. The stated goal for ClinicalStudyResults.org is to make clinical study results for U.S.-marketed pharmaceuticals more transparent.

- ClinicalTrials.gov

  In 1997, the FDA Modernization Act required the creation of a clinical trial database. In 2000, the National Library of Medicine (NLM) at the National Institutes of Health (NIH) announced the launch of ClinicalTrials.gov. The site provides regularly updated clinical trial registry of federally and privately supported clinical research in human volunteers.

- Current Controlled Trials (ControlledTrials.com

  Launched by biomedical publishing organization Star Navigation Group in 1998, the site's goal is to increase the availability and promote the exchange of information about ongoing controlled trials worldwide. The site is free to users. Sponsor organizations are charged to register their clinical trials.

- The Clinical Trial Registry Platform (http://www.who.int/ictrp/en/)

  The platform is a project of the World Health Organization (WHO). Its main components include:

- Norms and standards on which trials to register, what information needs to be registered, which is responsible for registration, etc. (Clinical trial result reporting is anticipated as a future platform attribute.)
- A network of Member Registers that meet WHO-specified criteria for quality and acceptability.
- A coordinated process for detecting and resolving duplicate registrations, and the assignment of a Universal Trial Reference Number to each unique trial worldwide.
- A one-stop search portal for searching registers worldwide.

- Thomson CenterWatch (centerwatch.com)

  Thomson CenterWatch is a publishing and information services company. Its website, centerwatch.com provides a list of IRB-approved clinical trials being conducted internationally. It provides free user access to information about clinical research, including listings of active industry and government-sponsored clinical trials, as well as new drug therapies in research and those recently approved by the FDA.

From Attributes to Content to Benefits: It's all about the User

Practicing physicians and their patients are key user groups of clinical trial registers so the value of a register must be measured in three ways: First, by its ability to provide up-to-date information directly related to clinical trial data and relevant to patient treatment. Second, by providing knowledge derived from trial data that is easily accessible and understood. Finally, the register's functionality must be intuitive so that anyone experienced with a standard Internet browser can quickly and easily navigate the site.

In addition to practicing physicians and their patients, other potential users span a broad spectrum of individuals and organizations integral to the medical science community. They include (but are not limited to) primary researchers; private, government, charitable and medical research sponsors; research funders; pharmaceutical companies; drug licensing agencies; medical science publishers; and research ethical review bodies.

To maximize the register's benefit to its users, the following attributes should be included:

- A single, comprehensive web-based repository accessible through a standard Internet browser;
- An assembly of detailed facts and findings of trials from private and public research institutions around the world;