ClinicalTrials.gov: An information resource to support your medical practice and provide treatment alternatives for your patients

By the Ad Hoc Committee on FDA Related Matters,
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Purpose

To provide college members a brief history and essential information about the National Institute of Health (NIH) sponsored clinical trial registry site "ClinicalTrials.gov". This information will guide college members to the use of the website and what information is available that can be used as a resource for their medical practice and support their patients in making informed treatment decisions.

Introduction

ClinicalTrials.gov is an easy-to-operate web site that offers up-to-date information for locating academic, federal and industry supported clinical trials for a wide range of diseases and conditions. ClinicalTrials.gov currently contains over 13,500 clinical studies sponsored by the National Institutes of Health, other U.S. federal agencies, academic institutions and private industry. Studies listed in the database are conducted in all 50 States and in over 100 countries. The intent of the web site is to communicate to physicians and patients with serious or life-threatening diseases the availability of clinical trials with experimental treatments for both drug and biological products.

History of ClinicalTrial.gov

In response to the U.S. public outcry for greater access to innovative and advanced medical treatments, the US Congress mandated that the National Institutes of Health (NIH) promptly and effectively communicate to patients, family members, health care professionals, and members of the public, information on clinical trials for a wide range of life-threatening or serious diseases and conditions. The information is to be provided in a timely and easily understood manner while updated on a regular basis to ensure public awareness. This mandate took the form of the Food and Drug Administration Modernization Act (FDAMA) that was passed into law by the U.S. Congress on November 27, 1997. This legislation now requires the U.S. Department of Health and Human Services, through the NIH, to establish a registry of clinical trials for both federally and privately funded clinical trials of "experimental treatments for serious or life-threatening diseases or conditions". The Food and Drug Administration Modernization Act (FDAMA) contains a number of sections related to the regulation of food, drugs, devices, and biological products but in particular, Section 113 - Information Program on Clinical Trials for Serious and Life-Threatening Diseases, requires the U.S. Department of Health and Human Services, through the National Institutes of Health, to establish a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and conditions conducted under FDA's investigational new drug (IND) regulations. The NIH, through its National

Library of Medicine (NLM) and with input from the FDA, developed a Clinical Trials Data Bank. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000 over the Internet. At that time, the data bank included primarily NIH-sponsored trials. In an effort to guide private industry to comply with the FDAMA law, the FDA has provided two draft guidance's and a final guidance to industry as to the process for providing clinical trial information to the Clinical Trial Data Bank. The first draft guidance provided recommendations for industry on the submission of protocol information to the Clinical Trials Data Bank. It included information about the types of clinical trials for which submissions are required under section 113 of the Modernization Act, as well as the content of those submissions. The second draft guidance addressed procedural issues, including how to submit required and voluntary protocol information to the Clinical Trials Data Bank, as well as proposed periods for submitting the information. A latest guidance, made available on January 2004 has combined all draft guidance's into a single guidance to industry.

As a result, the original Clinical Trials Data Bank has evolved to today's clinical trials registry web site (ClinicalTrials.gov) that is maintained by the U.S. National Institutes of Health (NIH), through its sister organization the National Library of Medicine (NLM) and in collaboration with the U.S. Food and Drug Administration (FDA).

How can ClinicalTrials.gov help to support your medical practice and provide treatment alternatives for your patients?

What information on the clinical trials is available to you?

The law directs the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health (NIH), to establish, maintain, and operate a data bank of information on clinical trials for drugs/biologics to treat serious or life-threatening diseases and conditions. The Clinical trial data bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other members of the public, and to health care providers and researchers. Specifically, section 113 of the Modernization Act requires that the Clinical trial data bank contain the following information in a form that can be readily understood by the public.

- Information about all Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions
- Description of the purpose of the experimental drug,
- Patient eligibility criteria for the study
- Location of clinical trial sites
- Point of contact to enroll in the trial

The FDA guidance recommends that any clinical trial conducted under an investigational new drug (IND) application for a drug to treat a serious or life-threatening disease or condition and is a trial to test the effectiveness must be included in the clinical trial

database. This also applies to non-US studies that are primarily being conducted outside of the US but are being conducted under the FDA IND regulations. Companies may also wish to include information on trials not designed to assess effectiveness or for drugs to treat conditions not considered serious or life-threatening. The abstract of the clinical study protocol must include a summary of the purpose of the study (in lay language), disease or condition and drug or therapy under study, research study design, phase of the trial, patient recruiting status (recruiting vs. no longer recruiting), criteria for patient participation (age, gender), site location of the trial and specific contact information for each site or a central contact person. The FDA requires that clinical study sponsors submit this information to the web site no later than 21 days after the trial is opened for enrollment. Any supplemental information can be added at 30-day intervals and may include amendments to the protocol, updated trial site listing or completion of patient enrollment. FDA strongly advises that information about clinical trials that are unexpectedly closed (e.g., put on clinical hold) be updated within 10 days. Finally, to ensure that the information is timely and accurate, FDA also advises sponsors to review and update all active protocol data on a semi-annual basis.

Who and how is a serious or life threatening disease or condition defined?

The FDA has defined the term "life-threatening" any diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival. The FDA has defined that the "seriousness" of a disease while a matter of medical judgment is generally based on factors such as survival, and the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. The FDA uses acquired immunodeficiency syndrome (AIDS), Alzheimer's disease, angina pectoris, heart failure, and cancer as serious diseases in their full manifestations. In addition, many chronic illnesses that are generally well managed by available therapy can have serious outcomes including inflammatory bowel disease in some or all of their phases.

How "early" in development, are these studies, as I do not want to put any of my patients in a clinical study where they may not gain any benefit?

In general, all of the drugs listed have completed their preclinical and Phase I human safety testing programs, and have been allowed to progress to the efficacy phase of clinical development. While safety of a drug continues to be monitored throughout all clinical studies, the studies listed in the database include all clinical trials designed to test the effectiveness of the drug or biologic in a given patient population. The FDA considers all phase 2, phase 3, and phase 4 clinical trials with efficacy endpoints to be trials to test effectiveness.

Is the website easy to use and does it provide sufficient information on clinical trials?

The web site is extremely easy to use and may be searched for clinical trials in several ways including by specific therapeutic areas such as gastroenterology, or for specific

diseases e.g. hepatitis. A list of all ongoing clinical studies for that disease will appear in a list form. By clicking on the study, all of the relevant information is displayed. Physicians and patients may also search for clinical studies by geographic location and limit studies to specific areas such as their home state. This information can be of significant use to the practicing physicians to know what studies are ongoing at local institutions specifically treating diseases of his/her specialty. The website also provides questions and answers to guide on searching the ClinicalTrials.gov database as well as finding studies on a particular disease or condition, specific treatments, or geographic location.

Physician should note that the website also provides patients with a basic tutorial on clinical research and includes explanations as to a series of basic questions that are inevitable asked by the patient during enrollment in a study. For example, what is a clinical trial, what is a protocol, what are clinical trial phases, what protections are there for participating in a clinical trial, what is informed consent, who can participate in a clinical trial, what are the benefits and risks of participating in a clinical trial, can I leave a clinical trial after it has begun? While the website does a good job in providing a basic overview of clinical research that is easily understood, it does not provide a substitute for patient to physician interaction that must occur to ensure the patient clearly understands the benefits and risks of participating in the clinical study, and how the study fits in the patient's overall treatment plan and any impact on concurrent illnesses. What the web site does provide to patients is a basic understanding of clinical research that allow the patient-physician conversation to focus on the disease, and risks and benefits where the physician adds the most value.

Impact on physician and patient interactions and treatment decisions?

To date this website has been a success for patients interested in participating in clinical trials. The FDA reports some 4 million visits to the site per month and averages over 17,000 hits per day. While this is a boon for patients interested in participating in research projects, but it is also presents complications for the practicing physician and represents a turning point in how we think about clinical research participation. Traditionally physicians have recommended specific clinical investigations to patients with qualifying diseases in an effort to provide treatment alternatives to more traditional approved therapies. The availability of this vast listing of clinical trials to the public is shifting the physician/patient interaction. No longer will participation be determined primarily by referrals from physicians. This new approach raises issues similar to ones that surfaced with direct marketing of prescription drugs to the public, and should be watched carefully to ensure we provide the best treatments for our patients.

Historically, whether or not a patient enters a research trial depends on a number of factors with the most important factor being their physician who informed their patients about available clinical trials and recommends that they participate in them. Obviously, the referrals from physicians require that they know about the relevant research. With thousands of clinical trials undertaken every year, it is understandable that physicians do not always know all the clinical research options for their patients. Since patients have

been largely dependent on their physicians for such information, the doctor's office can limit a patient's therapeutic options. ClinicalTrials.gov offers an easy way to deliver information about clinical trials to to both doctors and their patients. It effectively offers a catalog of the research trials available for particular diseases, for patients with specific diagnoses and in various regions of the country. This information should be the basis for the discussion with the patient on treatment alternatives and not the sole point of that discussion.

Conclusion

The demand by the public for better and timelier information about clinical trials has clearly shifted the way government policymakers view the public's participation in clinical research. In the 1970s, there were reports that subjects were exploited by clinical research without being adequately informed that the study held no medical benefit for them or were in situations that coerced their participation in the study. As a result, in 1981 the clinical research subject protection regulations were revised and based on the presumption that potential subjects needed primarily to be protected from the harms that research posed. Any medical benefits that subjects might realize from their participation in research were seen as a secondary outcome. Two decades later, this presumption has changed dramatically as FDA regulations now require inclusion of groups like women and minorities in research, based on the belief that there are real benefits from research participation, and that both individuals and the groups ought to have access to those benefits. With public policy shifting from protecting of patients from risk to assuring subjects prompt and timely access to the benefits of research participation, ClinicalTrials.gov will help facilitate that access by providing information about what research is being carried out. While the new Web site will certainly be a valuable tool for patients and their physicians, potential subjects must still be protected. It will be important to assure that the Web site will operate more as a clearinghouse for information and less as a means to simply attract research subjects to studies. It is important for the physician to continue to be involved in the overall treatment plan for their patients and to provide the detailed discussion on risks and benefits to their patient's participation in clinical research studies. ClinicalTrials.gov is a valuable information resource to support your medical practice and provide treatment alternatives for your patients.

ClinicalTrials.gov is available on the World Wide Web from the NLM Home Page (http://www.nlm.nih.gov/) or directly at ClinicalTrials.gov (http://clinicaltrials.gov/).