

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**CLINICAL TRIAL WEB SITES**

A Promising Tool to  
Foster Informed Consent



**JANET REHNQUIST  
INSPECTOR GENERAL**

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# ***OFFICE OF INSPECTOR GENERAL***

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# EXECUTIVE SUMMARY

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## PURPOSE

To assess the role of clinical trial Web sites in fostering informed consent and of institutional review boards in overseeing the information on these Web sites.

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## BACKGROUND

In a June 2000 report, *Recruiting Human Subjects: Pressures in Industry Sponsored-Clinical Research*, we examined the strategies sponsors and investigators use to recruit human subjects for clinical trials. In this report, we take a closer look at a new recruitment vehicle: clinical trial Web sites. These Web sites provide a significant opportunity not only to recruit human subjects, but also to foster informed consent by increasing the amount of information that is available to an individual interested in a clinical trial. In this report we focus on the latter opportunity. Given the central role institutional review boards (IRBs) have in ensuring informed consent, we also look at their role in overseeing the information on these Web sites.

In conducting this inquiry, we reviewed 22 clinical trial Web sites and 110 clinical trial listings on those sites. We analyzed both the general clinical trial information and the trial-specific information presented on these Web sites. We also interviewed Web site representatives, IRB members, and Federal officials.

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## FINDINGS

### **Clinical trial Web sites are emerging as an important recruitment strategy.**

Clinical trial Web sites are growing in popularity. Total visitors on the National Cancer Institute's Web site, CancerNet, increased from an average of 500,000 visitors per week in May 2000 to an average of 700,000 visitors per week in May 2001. Another site, CenterWatch, saw the average number of visitors increase from 38,000 in 1997 to 334,000 in 2000.<sup>1</sup> Furthermore, these Web sites offer benefits as a recruitment vehicle: access to a large number of individuals, services that allow for personalization, and the potential to reduce costs associated with recruitment.

## **Clinical trial Web sites show promise as a means of fostering informed consent.**

**Most of the Web sites we reviewed provide valuable general and trial-specific information about clinical trials.**

In our review of general clinical trial information on 22 Web sites we found that:

- ▶ 21 explain the importance of informed consent.
- ▶ 16 describe the role of IRBs in protecting human subjects.
- ▶ 16 explain the overall purpose of clinical trials.

In our review of trial-specific information in 110 clinical trial listings we found that:

- ▶ 91 provide eligibility criteria.
- ▶ 80 provide a clear statement of the trial's purpose.

## **But clinical trial Web sites fail to take full advantage of their potential to foster informed consent.**

**Most of the clinical trial listings we reviewed exclude key information.** In our review of 110 clinical trial listings, we found shortcomings in the following areas:

- ▶ **Trial benefits and risks.** Not one has any information about risks to human subjects, while 29 describe the benefits.
- ▶ **Sponsor name.** 77 fail to identify the sponsor for the clinical trial.
- ▶ **Phase of trial.** 69 do not indicate the phase of the clinical trial.
- ▶ **Description of trial.** 56 lack a general description of the protocol.

**Some Web sites provide misleading general clinical trial information.** For example, one Web site inaccurately describes phase one trials by saying the chances of a successful treatment are good, when in fact such trials are conducted to test safety. Another suggests that clinical trials provide access to new drug treatments, when in fact they involve the use of experimental drugs, not proven treatments.

**Most Web sites that collect personal information fail to disclose how they will use the information.** In our review of 13 online privacy policies from Web sites that collect personal information, we found that:

- ▶ 11 do not indicate how long the Web site stores such information.
- ▶ 9 do not describe their processes to ensure that such information is securely transmitted over the Internet.

**Web sites provide minimal information about their financial relationships.** Of the 12 Web sites that generate revenue, half fail to disclose how they do so.

### **IRBs face major challenges in reviewing clinical trial Web sites.**

Federal guidance for IRBs fails to make clear when a clinical trial listing requires review and fails to address privacy issues surrounding prescreening through the Internet. IRBs have limited leverage over general information on Web sites because it is outside their purview. Finally, many IRBs are already overburdened by increased workloads and lack the resources to take on the additional responsibility of reviewing clinical trial listings.

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## **RECOMMENDATIONS**

We direct three recommendations jointly to FDA and the Office for Human Research Protections (OHRP). Both of these entities issue guidance to IRBs and rely on them to ensure adherence to federal regulations that afford protections to human subjects.

### **IRB OVERSIGHT. Provide further guidance to IRBs on clinical trial Web sites.**

Clarify that risk and benefit information in trial listings should be subject to IRB review and approval. In addition, any prescreening used for specific trials that collect personal information should be reviewed and approved by an IRB. In reviewing prescreening mechanisms specific attention should be given to privacy and confidentiality issues.

### **VOLUNTARY STANDARDS. Facilitate the adoption and use of voluntary standards for clinical trial Web sites.**

Through workshops and other forums for deliberations, FDA and OHRP should exert leadership to foster the development and application of voluntary standards for clinical trial Web sites. On the basis of our inquiry, we suggest four standards that focus on maximizing the Web site's potential to foster informed consent. They call for a comprehensive overview of clinical trials, key information in clinical trial listings, and prominent disclosure of privacy policies and significant financial relationships (see page iv). The standards go beyond the risk-benefit and prescreening information for which we call for mandatory IRB review and approval.

### **INDEPENDENT REVIEW. Encourage clinical trial Web sites to undergo periodic review by independent bodies.**

Periodic review of clinical trial Web sites will help ensure that information provided by them is balanced and not misleading or coercive. These reviews could address general clinical trial information provided on the Web sites and examine their privacy policies and procedures surrounding personal information. Reviews could be conducted by IRBs and/or accrediting bodies.

## Standards for Clinical Trial Web Sites: A Preliminary Framework

Standards		Elements
<b>General Clinical Trial Information</b>	<p><i>Provide a comprehensive overview of clinical trials</i></p> <p>The more subjects know about the process in general the more informed their decision to enroll will be.</p>	<p>A comprehensive overview includes:</p> <ul style="list-style-type: none"> <li>▶ Clear statement that a clinical trial is research not treatment</li> <li>▶ Description of FDA's drug approval process</li> <li>▶ Description of the Common Rule and FDA Good Clinical Practice regulations</li> <li>▶ Description of the informed consent process</li> <li>▶ Description of the role of IRBs</li> <li>▶ Explanation of the importance of weighing risks and benefits</li> <li>▶ Information on how to contact key Federal agencies for further clinical trial information</li> <li>▶ Sources of clinical trial information</li> <li>▶ Explanation of the importance of considering alternatives to a clinical trial.</li> </ul>
	<p><i>Disclose prominently a comprehensive privacy/confidentiality policy</i></p> <p>Disclosure gives consumers control over their personal information before they share it. Consumers should be fully aware of how their personal information will be used.</p>	<p>A comprehensive policy contains the following with regards to personally identifiable information:</p> <ul style="list-style-type: none"> <li>▶ How long is personal information retained</li> <li>▶ What information is collected</li> <li>▶ How information will be used</li> <li>▶ What entities or individuals have access</li> <li>▶ How consumers can eliminate personally identifiable information</li> <li>▶ When the policy was last updated</li> </ul>
	<p><i>Disclose prominently significant financial relationships</i></p> <p>Informs the subject of potential conflicts of interest the Web site may have.</p>	<p>Significant financial relationships include:</p> <ul style="list-style-type: none"> <li>▶ Revenues collected based on Web site services</li> <li>▶ Funding the site receives from pharmaceutical companies, health insurers, trial sites, etc.</li> <li>▶ Agreements for advertising on the site</li> </ul>
<b>Trial-Specific Information</b>	<p><i>Provide key information in clinical trial listings</i></p> <p>Key information about specific trials helps the subject more quickly identify appropriate trials.</p>	<p>Key trial information includes:</p> <ul style="list-style-type: none"> <li>▶ Title</li> <li>▶ Phase</li> <li>▶ Purpose</li> <li>▶ Description of trial</li> <li>▶ Eligibility criteria</li> <li>▶ Duration of trial</li> <li>▶ Time commitment for the subject</li> <li>▶ Balanced description of risks and benefits</li> <li>▶ Compensation for injury</li> <li>▶ Name of trial sponsor(s)</li> <li>▶ Name of clinical investigator(s)</li> <li>▶ Contact information for research site(s) - contact name, phone number, and location</li> </ul>
<b>SOURCE:</b> Office of Inspector General.		

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## COMMENTS ON THE DRAFT REPORT

We received comments on the draft report from the Food and Drug Administration, the Office for Human Research Protections, and the National Institutes of Health. Each agreed with the thrust of our report and offered a number of comments. Below we summarize their comments and, in italics, offer our response to them. In this final report, we made some technical changes and clarifications in response to the comments. The full text of the comments appears in Appendix E.

### Food and Drug Administration

The Food and Drug Administration indicated that it will be addressing our recommendations as it revises its Information Sheets for IRBs and Clinical Investigators. However, FDA expressed concern about the potential burdens to the already overburdened IRBs. As a way of easing the burden, it suggested that Federal guidance might call for IRBs to limit their reviews of trial-specific information to that information not considered basic trial information. *We modified our recommendations to focus IRB review and approval to the risk and benefit information and prescreening questions for trial listings.*

### Office for Human Research Protections

The Office for Human Research Protections emphasizes that clinical trial web sites have not only the potential, but also a requirement to foster informed consent. Even basic trial information, it states, is subject to IRB review. If further guidance is needed to make this clear, it urges that it be issued. *OHRP's response focused on Web sites for institutions that received federal funds and are under the purview of those institutions. Our review included these sites but also others that are not part of any research institution. We suggest that FDA and OHRP work together to produce a common set of expectations for all Web sites. The preliminary standards we propose may be helpful in this regard.*

### National Institutes of Health

The National Institutes of Health, among a number of technical comments, asked for further clarification addressing the IRB's responsibility for Web site trial listings beyond the local sites. *In our report, we added language specifying that a local investigator or a sponsor initiating a trial listing that includes more than basic trial information is responsible for obtaining IRB approval.*

# TABLE OF CONTENTS

<b>EXECUTIVE SUMMARY</b> .....	i
<b>INTRODUCTION</b> .....	1
<b>CLINICAL TRIAL WEB SITES: AN OVERVIEW</b> .....	4
<b>FINDINGS</b>	
Emerging Importance for Recruitment Strategy .....	5
Promising Means of Fostering Informed Consent .....	7
Shortfalls of Clinical Trial Web Sites .....	10
Challenges Facing IRBs .....	13
<b>RECOMMENDATIONS</b>	
IRB Oversight .....	16
Voluntary Standards .....	17
Independent Review .....	17
<b>COMMENTS ON THE DRAFT REPORT</b> .....	19
<b>APPENDICES</b>	
A: Main Players in Clinical Research .....	20
B: Best Practices of Clinical Trial Web Sites .....	21
C: Standards from Health Internet Organizations .....	27
D: Summary Data of Web Site Review .....	31
E: Full Text of Comments on the Draft Report .....	34
F: Endnotes .....	40
<b>ACKNOWLEDGMENTS</b> .....	44



# INTRODUCTION

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## PURPOSE

To assess the role of clinical trial Web sites in fostering informed consent and of institutional review boards in overseeing the information on these Web sites.

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## BACKGROUND

Clinical investigators and sponsors of clinical trials, typically pharmaceutical companies, often have difficulties finding a sufficient number of human subjects to participate in clinical trials (see appendix A for an overview of the clinical trial process). These difficulties slow down the process of bringing new drugs to market, increase costs, and delay access to new and potentially useful drugs. In a June 2000 report, *Recruiting Human Subjects: Pressures in Industry Sponsored-Clinical Research* (OEI-01-97-00195), we examined the strategies sponsors and investigators use to recruit human subjects. In this follow-up report, we look at a new recruitment vehicle: clinical trial Web sites (see primer on page 4). Given the central role institutional review boards (IRBs) have in ensuring informed consent, we also look at their role in overseeing the information on these Web sites.

### Web sites as an Opportunity to Recruit Human Subjects

The Internet offers clinical trial Web sites a unique opportunity for clinical investigators and sponsors to target individuals with an interest in clinical trials. These Web sites are portals for clinical trial information that can be accessed anytime by any individual with access to the Internet. In this report, we begin by offering some background on the growth of these Web sites and the factors propelling them as a recruitment vehicle.

### Web Sites as an Opportunity to Foster Informed Consent

No less significant than the above opportunity is the one that these Web sites offer to facilitate informed consent among those individuals who decide to become human subjects in a clinical trial. These Web sites have an opportunity to raise the awareness and understanding of clinical trials by increasing the amount of information available to these individuals and, thereby, fostering informed consent. It is this opportunity that serves as the main focus of this report.

Obtaining informed consent has long served as one of the bedrock elements of protecting human subjects. In 1978, the influential *Belmont Report*, issued by the National Commission for the Protection of Human Research Subjects, set forth three essential

elements to informed consent: (1) information — accurate and balanced information that helps individuals make a reasoned decision to participate or not; (2) comprehension — information presented in ways that facilitate understanding; and (3) voluntariness — information presented under conditions free of coercion and undue influence.<sup>2</sup>

Clinical trial Web sites afford an opportunity to foster informed consent that can help meet the elements outlined in the *Belmont Report*. These sites provide access to both general and trial-specific information. The Internet allows individuals as much time as they need to thoroughly review and comprehend this information. Web sites can foster informed consent by presenting clinical trial information that helps individuals make balanced assessments of risks and benefits and prepare questions for clinical investigators, research coordinators, and their own physicians. These sites are not a substitute for the discussion that takes place between the individual and physician, but an opportunity to raise the awareness and increase the amount of information that is available prior to signing the informed consent document. This opportunity is especially important because the informed consent process is too often one that occurs in a hurried fashion under intimidating surroundings and confronts the potential subject with a detailed, lengthy document to sign — one that often appears aimed more at the legal liability concerns of the institution or sponsor than to the concerns of the potential subject.<sup>3</sup> Informed consent of this kind inhibits the comprehension or voluntariness envisioned in the *Belmont Report*.

## Relevance to Federal Oversight

Within the Department of Health and Human Services, two components have the primary responsibility of helping to ensure the rights and welfare of human subjects participating in clinical research. The Food and Drug Administration (FDA) regulates research in the products it regulates. The Office for Human Research Protections (OHRP) within the Office of the Secretary ensures the rights and welfare of human subjects participating in research funded by HHS. Both entities rely heavily on IRBs for ensuring adherence to Federal regulations that protect human subjects.<sup>4</sup> These boards conduct initial and continuing reviews of research protocols, informed consent documents, and recruiting practices. FDA and OHRP issue guidance documents to help IRBs, sponsors, and investigators meet the Federal requirements.

## Methodology

Our inquiry analyzed 22 Web sites and 110 clinical trial listings. The exact number of clinical trial Web sites is unknown because of the vast and constantly changing nature of the Internet. Therefore, we researched relevant literature and interviewed key stakeholders to select a sample of 22 Web sites that is largely made up of third-party sites, but also includes Federal sites, location-specific sites, and sponsor-specific sites (see appendix D for a complete listing of the 22 Web sites).<sup>5</sup> For our review of clinical trial listings, we selected five listings from each of the 22 Web sites, for a total of 110. The sample of listings represents various drug trials for

life-threatening diseases and chronic illnesses. We did not review other practices of Internet recruitment such as Web sites that are specific to one trial and banner advertisements.

We reviewed two types of information from each Web site in our sample: general clinical trial information and trial-specific information. We reviewed each of the 22 Web sites for the types of general clinical trial information they provide, such as a description of Federal regulations and the process of informed consent. We reviewed our sample of 110 clinical trial listings for the types of trial-specific information they provide such as title, purpose, and contact information. We did not evaluate functionality or accuracy of information of the Web sites. (See appendix D for all data elements.)

We conducted interviews with key representatives from 10 of our sample Web sites to answer broader questions and provide greater context. Interviews included discussions about the advantages and disadvantages of Internet recruitment, Federal guidance, and the role of IRBs. In addition, we interviewed Federal officials at OHRP and FDA, IRB members, privacy and patient advocates, and ethicists.

This report reflects the information that these Web sites provided during the period of April 2001 through September 2001. Since our review of these Web sites, some have changed in appearance and content.

We conducted this study in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

# A PRIMER ON CLINICAL TRIAL WEB SITES

## What kind of information do Web sites provide?

**General Clinical Trial Information.** This can cover a wide range including, but not limited to, information on the elements of clinical trials and the drug approval process such as the protections afforded to human subjects participating in trials, the definitions of key medical and research terms, and the standard treatments, therapies, and the state of research for particular diseases.

**Trial-Specific Information.** Clinical trial listings on these Web sites provide specific information about trials enrolling subjects. The information is likely to include the title, purpose, eligibility criteria, and contact information.

## What types of Web sites exist?

**Federal Sites.** Three such sites are: (1) The AIDS Clinical Trials Information Service (ACTIS) offers a database of AIDS clinical trials; (2) CancerNet provides a database of cancer clinical trials, and (3) ClinicalTrials.gov presents a listing of all federally and some privately funded clinical research.<sup>6</sup> The National Institutes of Health maintains these three sites.

**Third-Party Sites.** These sites are not operated by funders, sponsors, or by the institutions at which trials are being carried out. They tend to be operated by private companies. The information on them is typically copyrighted. Most of the trial listings on these sites are copied from Federal sites (in some cases the Web site will edit the Federal trial descriptions). Sites also obtain trial information directly from sponsors and clinical investigators. In a few instances, sites create their own clinical trial descriptions, drawing on non-copyrighted sources. These sites generate revenue in the following ways: (1) fee-per listing (a flat fee to list a single trial); (2) fee-per-referral (a fee levied each time an individual contacts the trial location through the site); (3) fee-per-enrollment (a fee for each subject that ends up enrolling in a trial ; and (4) fee for data access (a charge to outside entities seeking access to the site's databases that maintain information on individuals who use the site); and (5) fee for advertising on the site.

**Location-Specific Sites.** A specific healthcare facility or its contractor manages these sites and mainly list clinical trials being conducted at their location. Trial information tends to be obtained directly from the clinical investigators at those locations.

**Sponsor-Specific Sites.** Commercial sponsors of clinical trials or their contractors manage these sites. Trials listed on these sites tend to be only those trials supported by the sponsor. Information on the site is provided by the sponsor or contractor; the clinical investigators are not necessarily involved with or even aware of this process.

**Others.** These include sponsor and location-specific sites, as well as patient advocacy sites.

## What Kind of Services do the Web Sites Provide?

**Prescreening.** There are two types: *General Prescreening for Clinical Trial Listings*, an online questionnaire used to generate a list of clinical trials an individual may be eligible for, and *Prescreening for a Specific Trial*, an online questionnaire used to determine if an individual is eligible for a particular clinical trial. If the individual is eligible, then, depending on the site, the individual or the Web site may contact the clinical investigator to discuss enrollment.

**Disease Information.** Offers information concerning specific diseases.

**Trial Folders.** Enable users to save specific trials of interest and access them later through a password.

**E-Mail Updates.** Provide notices that alert users to new trials and information available on the site.

**Message Center.** Allows users to access, via a password, messages in areas of particular interest.

**Chat Rooms.** Allows users to discuss with one another about various health-related topics.

# FINDINGS

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## Web sites are emerging as an important recruitment strategy.

### Clinical trial Web sites are growing in popularity.

**Increasing number and variety of Web sites.** Over half of the 22 Web sites we reviewed were created in the last 5 years. The Federal government took the lead in using the Internet to provide clinical trial information to the public and is still a major player, despite the entrance of various privately run Web sites. Entrepreneurs are starting companies focused on recruiting human subjects over the Internet. Pharmaceutical companies and contract research organizations are listing clinical trials on their own Web sites as well as listing trials on other clinical trial Web sites. Research institutions such as academic medical centers are creating their own Web sites that list trials currently enrolling subjects at their institution.

**Increasing use of clinical trial Web sites.** Total visitors on the National Cancer Institute's Web site, CancerNet, increased steadily during the last year.<sup>7</sup> The site averaged about 500,000 visitors per week in May 2000 and increased to 700,000 visitors per week in May 2001. Another popular Web site, CenterWatch, saw the average number of visitors increase from 38,000 in 1997 to 334,000 in 2000.<sup>8</sup> Similarly, the government-sponsored AIDS Clinical Trials Information Service, ACTIS, averaged 6,084 visitors per month in 1999. Within 2 years this number more than doubled to about 12,580 visitors per month.<sup>9</sup>

Research professionals that use the Internet for recruiting patients are also contributing to the increase of visitors to these Web sites. According to a recent survey of sponsors and contract research organizations conducted by the Association for Clinical Research Professionals, 15 percent of the respondents regularly use the Internet to recruit patients and by 2001 over half of the respondents expect to use the Internet regularly to recruit patients.<sup>10</sup>

Three basic trends drive the growth of the number of visitors to clinical trial Web sites. First, consumers are taking an increasingly active role in managing their health care. According to a recent survey of human subjects, 54 percent self-referred themselves into a trial.<sup>11</sup> Second, physicians are beginning to incorporate the Internet into their profession. A recent poll showed that from 1999 to 2001, physician use of the Internet went up from 34 percent to 40 percent.<sup>12</sup> As physicians become more accustomed to using the Internet, they will likely use it to search for clinical trials for their patients as well as encourage their patients to do so on their own. And finally, the growing accessibility and use of the Internet, in general, is fueling the number of visitors to clinical trial Web sites.

## Clinical Trial Web sites offer several benefits as a recruitment vehicle.

Representatives from clinical trial web sites estimate that these sites enroll between 10-15 percent of the subjects in a particular trial. They anticipate that the percentage of enrollees from the Internet will increase as the sites become more widely used. Below we identify three advantages that these sites offer as a recruitment vehicle.

**Accessibility.** In the latter half of 2000, over 100 million adults accessed the Internet.<sup>13</sup> An estimated 60 million people used the Internet to seek health or medical information.<sup>14</sup> The Web sites make clinical trial information accessible to anyone on the Internet. The anonymity that many of the sites offer may further encourage the use of these Web sites by individuals who may not have otherwise done so out of concern for privacy or confidentiality.

Clinical trial Web sites have made information particularly accessible to vulnerable populations who are often desperate for medical options. Many of these Web sites have taken great strides to make clinical trial information accessible to those suffering from a chronic or life-threatening illness such as AIDS or cancer, especially where standard medical treatment has failed. “Cancers and other Neoplasms” is the largest disease category on ClinicalTrials.gov offering 2,103 trials out of the 11,000 trials available on the Web site.<sup>15</sup> One Web site we reviewed, EmergingMed, is devoted entirely to cancer trial listings.

Clinical trial Web sites also improve access to clinical trial information for rare diseases. Identifying potential subjects for rare disease trials is difficult for sponsors and investigators since the population is small and the diseases are less known. Individuals with rare diseases often do not hear about trials, especially if they are far from a large medical center. These Web sites can provide people all over the country with access to rare disease information and clinical trial locations. “Rare Diseases” is the second largest disease category on ClinicalTrials.gov with 1,901 trials.<sup>16</sup>

**Personalization.** The Internet allows Web sites to customize the information and services they provide to individuals (table 1). One of the most advantageous services is prescreening. Many of these Web sites contain hundreds and, in some cases, thousands of trial listings. Prescreening uses personal information that is submitted by individuals to determine their eligibility for one or more trials. An effective prescreening process can quickly bring together a potential subject and investigator and help ensure timely enrollments. Other services such as chat rooms and e-mail updates help keep individuals abreast of new information as well as offer support.

<b>Personalized Services</b>	<b>Number of Web Sites</b>
Prescreening	8
Personal folders	6
E-mail updates	12
Chat rooms	2

**Cost effectiveness.** On average, recruitment accounts for 10-15 percent of the overall research study budget.<sup>17</sup> Traditional advertising, print or television, can be one of the more expensive recruitment strategies and can cost, on average, over \$600 dollars per patient enrolled.<sup>18</sup> The Internet can disseminate information relatively inexpensively and reduce the costs associated with recruiting. One case study estimated Internet recruitment costs at \$63 per enrolled patient — less than half the cost of other recruiting strategies used for the study.<sup>19</sup>

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## **Clinical trial Web sites show promise as a means of fostering informed consent.**

### **Most of the 22 Web sites we reviewed provide valuable general clinical trial information.**

Below we demonstrate how clinical trial Web sites can help foster informed consent by providing key general information to potential subjects. In our review of 22 Web sites we found that:

- ▶ 21 explain the importance of informed consent as a means to help subjects make an informed decision about whether to participate in a clinical trial.
- ▶ 16 describe the role of IRBs in protecting human subjects.
- ▶ 16 explain the overall purpose of clinical trials is to learn about a new drug or diagnostic test, not to treat patients.
- ▶ 12 describe clinical trials as part of the FDA's drug approval process to evaluate the safety and efficacy of drugs.
- ▶ 12 explain the importance of weighing the risks and benefits associated with a clinical trial when considering to participate.

However, these Web sites vary in the extent of information they provide. For example, we found one site that describes the role of IRBs in a single sentence, compared with another that devotes an entire paragraph to the subject and even elaborates on the importance of IRB members avoiding conflicts of interest.

Below are two examples we selected from Web sites that demonstrate the promise that these sites offer to foster informed consent. One explains the role of IRBs (figure A); the other clearly states that trials may have risks as well as possible benefits (figure B). (For more examples of promising approaches see appendix B.)

### Figure A: Explaining the Role of IRBs

#### What is the basic objective of IRB's?

IRB's are comprised of medical professionals as well as nonmedical professionals and laypersons who review all research with the basic objective to protect trial participants. Specifically, they try to uphold 3 principles, **respect for persons**, **beneficence**, and **justice**.

- **Respect for persons** requires them to assure that patients are provided with all of the information they need in order to decide if they should enroll
- **Beneficence** requires them to protect the patients from harm, and maximize the potential benefit
- **Justice** requires that participants not assigned at random to the new drug, device, or procedure be offered usual medical care of proven benefit.

Source: thehealthexchange.org (6/25/01)

### Figure B: Explaining Risks Associated with Clinical Trials

#### Are there risks in clinical trials?

The process of evaluating new treatments can involve some risk. All drugs used in clinical trials have been extensively tested in laboratory experiments. However, some side effects do not become apparent until the treatments are given to humans. Side effects can vary from patient to patient. It is important to remember that clinical trials can carry unknown dangers as well as possible benefits.

Source: Veritas Medicine (3/29/01)



## Most of the 22 Web sites we reviewed provide important trial-specific information.

In our review of 110 clinical trial listings we found that:

- ▶ 91 (83 percent) provide eligibility criteria. This type of information is important because it discourages individuals from inquiring about trials for which they are not eligible, thereby, allowing individuals to focus their time on understanding information in those trial listings that are most relevant to them.
- ▶ 80 (73 percent) provide a purpose statement. A purpose statement can indicate the type of experimental drug being tested, the type of subjects needed, and further emphasize that a clinical trial is research, not treatment.

Similar to general information, the extent of trial-specific information varies from site to site. For example, one Web site we reviewed provides several paragraphs of eligibility criteria that included sex, disease, age, previous medications and surgical treatments, and stage of disease, while another Web site for the same trial only offers sex, age, and disease information.

We highlight two examples from Web sites that use novel approaches to present clinical trial listings in an easy format that fosters comprehension. (For additional examples of promising approaches see appendix B.) One provides an interactive listing that links to a glossary of terms. Within each listing, selected words are underlined to indicate they are active links to the National Cancer Institute's dictionary of cancer terms (figure C). The other example shows how the interactive capability of the Internet can allow individuals to link from the trial listing to other sources of information such as relevant journal articles (figure D on following page).

### Figure C: Defining Clinical Trial Terms

**Rationale:** Drugs used in chemotherapy use different ways to stop tumor cells from dividing so they stop growing or die. Combining more than one drug and combining radiation therapy with chemotherapy may kill more tumor cells.

**Purpose:** Phase I trial to study the effectiveness of combination chemotherapy consisting of uracil, tegafur and leucovorin plus radiation therapy in treating patients with colorectal cancer who have undergone surgery to remove the tumor.

Source: Cancernet (7/16/01)

## Figure D: Providing Background Information on a Clinical Trial

**More Information**

[Detailed Web Page](#)

**Publications:**

[Young, 1999. Acquired aplastic anemia. JAMA, Vol. 282, p. 271](#)

[Young, 1997. The pathologic biology of acquired aplastic anemia. N Engl J Med, Vol. 335, p. 865](#)

[Fader, 1994. An increased HLA-DRE frequency is seen in aplastic anemia patients. Blood, Vol. 84, p. 922](#)

Source: ClinicalTrials.gov (7/16/01)

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## But clinical trial Web sites are not taking full advantage of their potential to foster informed consent.

### Most of the clinical trial listings we reviewed exclude key information.

Web sites provide trial-specific information in listings to draw in those people who may be potential study subjects. It is important, especially from the outset, that this information be accurate and comprehensive. If not, then potential subjects may enter the informed process with false impressions, thereby undermining that process.

In our review of 110 clinical trial listings, we found that:

- ▶ None describe the risks associated with the study protocol, while 29 describe the benefits to subjects. It is important that risks and benefits are presented to subjects in a balanced fashion. Listings that only provide benefits can mislead individuals to assume that the trial is without risks. We found that most of the benefits described were not therapeutic, but instead focused on convenience and incentives to the study subject, such as free parking and monetary compensation. These benefits can be misleading if not tempered by a statement that risks are involved.
- ▶ 77 (70 percent) fail to identify the sponsor for the clinical trial. The name of the sponsor tells the individual who is accountable for the study.

- ▶ 69 (63 percent) do not indicate the phase of the clinical trial. Thus, in these cases, an individual would not be able to distinguish a phase one trial aimed strictly at testing the safety of an experimental drug from a phase three trial focused on testing efficacy as well as safety.
- ▶ 56 (51 percent) lack a general description of the protocol. A general description provides a sense of the procedures that a subject will undergo and the time commitment that is necessary to participate in the trial.

### **Some clinical trial Web sites we reviewed provide misleading information that can undermine informed consent.**

In our prior reports we found traditional advertisements that overstated benefits to recruit human subjects.<sup>20</sup> Therefore, it is not surprising that we also found this to be a problem on several clinical trial Web sites. Below we cite some examples of misleading general information that we found on three different Web sites. In each case we explain our basis of concern:

#### **Example #1**

**Web Site Text:** “Why should I participate in a clinical trial?...Often [taking part in a research study] gives you the chance to access a medicine that is not available on the market for prescription.”<sup>21</sup>

**Basis for Concern:** This statement neglects to mention that the medicine has not yet been shown to be safe and effective, which is why it is not on the market.

#### **Example #2**

**Web site Text:** “Is a clinical trial right for you?...Many people who volunteer for studies do so because it provides them access to new drug treatments before they are available in the marketplace.”<sup>22</sup>

**Basis for Concern:** Similarly, this statement neglects to mention that the medicine has not yet been shown to be safe and effective and that the main objective of clinical trials is not about access, but about research.

#### **Example #3**

**Web site Text:** “Clinical trial phases...In general, the chances of success in a phase I trial are good...”<sup>23</sup>

**Basis for Concern:** Phase one trials are not designed to show efficacy; they are designed to show that the drug is not toxic in humans. Little is known about the safety

of drugs in phase one trials, because this is when they are usually tested in humans for the first time or are evaluations of a new dosage or new mode of administration.

### **Most clinical trial Web sites we reviewed that collect personal information fail to disclose how they will use the information.**

Of the 22 Web sites we reviewed, 13 collect personal information and each of them provide an online privacy policy. However, in our review of these 13 online privacy policies we found that:

- ▶ 11 do not indicate how long the Web site stores personal information.
- ▶ 9 do not address their processes to ensure that personal information is securely submitted over the Internet.
- ▶ 7 do not specify whether personal information is shared with an investigator or a clinical research personnel at the trial location.
- ▶ 6 do not provide a linking policy that addresses privacy concerns when users leave their Web site and link to a different site. Lack of a linking policy is worrisome because linking from one site to another can appear seamless and individuals may be unaware that they have left the original site.

Collecting personal information such as health information is not necessarily inappropriate. In fact, many individuals are willing to share such information in return for possible benefits. The issue of concern from the perspective of protecting human subjects is whether users are fully aware of how their personal information will be used prior to submitting it to the Web site.

### **Clinical trial Web sites provide minimal information about their financial relationships.**

Of the 12 Web sites that generate revenue, half fail to disclose how they do so. Knowledge of a Web site's financial relationships can affect how an individual interprets information on that Web site. Of those Web sites that do disclose their revenue sources, three indicate that they generate revenue from patient enrollment/referral fees and three indicate that they generate revenue from trial listing fees. Aside from addressing revenue based on patient enrollment and listing fees, only one Web site clearly states it does not accept funds from pharmaceutical companies and another site states it does not accept advertising. Three Web sites do accept advertisements and provide a corresponding advertisement policy.

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## **IRBs face major challenges in reviewing clinical trial Web sites.**

Institutional review boards (IRBs) are the only entities whose sole function is to ensure human-subject protections.<sup>24</sup> They play a critical role in safeguarding subjects' rights and welfare during the recruitment process, informed consent process, and the conduct of the trial.

### **Limited Federal guidance on trial-specific information.**

Both FDA and OHRP have issued guidance documents to sponsors, investigators, and IRBs regarding recruitment practices. Current FDA guidance addressing clinical trial listings on the Internet is part of a broader commentary about recruitment that is addressed in the 1998 FDA Information Sheet, "Recruiting Study Subjects." OHRP's guidance is contained in its 1993 Institutional Review Board Guidebook and endorses the aforementioned FDA Information Sheet. Because the two guidance documents are identical, we will refer to them together as Federal guidance.

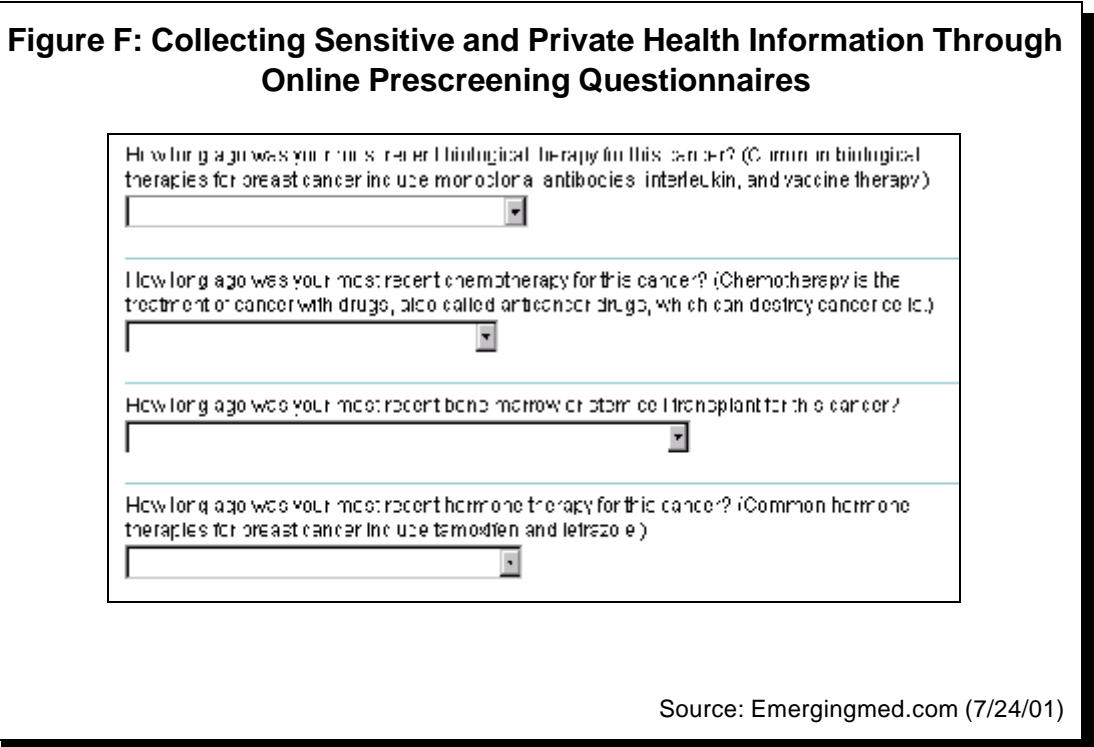
**Unclear language determining when a clinical trial listing requires review.** Federal guidance calls for IRBs to review and approve all direct advertisements to study subjects.<sup>25</sup> However, the guidance carves out an important exemption for clinical listing services. It states that clinical trial listing services that contain basic trial information do not need to be reviewed by an IRB. It adds that basic trial information includes: title, purpose, protocol summary, basic eligibility criteria, study site location, and how to contact the site. The guidance specifically mentions the National Cancer Institute's cancer trial listing, the Physician's Data Query (PDQ) found on CancerNet, and the government-sponsored AIDS information service, ACTIS, as examples of clinical trial listing services that contain basic trial information and do not require IRB review.

However, many of the clinical trial Web sites in our review provide additional trial information in their listings that is not explicitly mentioned in the guidance as basic trial information, such as risks and benefits and the name of the investigator or sponsor. It is unclear whether this type of trial-specific information is considered to be basic trial information. If it is not basic trial information, then according to current guidance it requires review by an IRB. Although some investigators, sponsors, and Web sites submit clinical trial listings for review regardless of whether they contain basic trial information, most do not appear to do so.

### **Failure to address privacy issues surrounding prescreening for specific trials.**

Prescreening for a specific trial uses a questionnaire that asks individuals to answer personal questions to determine whether they are eligible for particular trials (see figure F on the following page for sample questions). The personal information collected through prescreening raises concerns about privacy and confidentiality.

Although prescreening through the Internet is new, the concept of prescreening is not. Online prescreening questions are similar to those on scripts that are used by telephone receptionists at central call centers for determining eligibility for a specific study. Federal guidance has long required receptionist scripts to be reviewed by an IRB to ensure that individuals' confidentiality and privacy are protected. However, the guidance does not require online prescreening processes, which contain the same type of sensitive questions as receptionists' scripts, to be reviewed by an IRB.



### Limited leverage over general clinical trial information.

The general information on a clinical trial Web site is of considerable relevance to the informed consent process. It can, as we have suggested, help individuals gain valuable perspectives on the pros and cons of clinical trials and on the protections that are supposed to be afforded to human subjects. As noted earlier, it can also serve as a means of misleading potential subjects — for example, by indicating that trials present an opportunity to gain access to new drugs.

Notwithstanding the significance of the information presented at this general level, it exists in a domain that is beyond the purview of IRBs. Federal regulations do not require the IRBs to review this information. The limited attention that IRBs give to Internet recruitment is, therefore, limited almost entirely to trial-specific information.

## **IRBs are overburdened.**

Some IRB members that we spoke with require investigators to submit for review clinical trial listings that will be posted on Web sites. They also anticipate more Internet-based recruitment in the future and expressed concerns about how to address the increasing use of this strategy. In a prior report we drew attention to the fact that IRBs are reviewing more materials at a faster pace.<sup>26</sup> We also found that 25 percent of IRBs do not even ask investigators to explain their recruiting practices.<sup>27</sup>

Many IRBs are already burdened by increased workloads and lack the resources to devote to reviewing traditional recruitment materials. The nature of the Internet allows for vast amounts of information to be published and updated relatively inexpensively. Some trial listings on the Web can be four pages long and contain numerous links to other Web sites that provide even more information. Thus, clinical trial listings contain more information than a typical print advertisement and review of them will likely add to IRB workloads.

# RECOMMENDATIONS

In this inquiry we focused on the potential that clinical trial Web sites have to foster informed consent. Below we recommend steps that can be taken to use this potential and help ensure that information on these Web sites does not undermine informed consent. We direct our recommendations jointly to the Food and Drug Administration (FDA) and to the Office for Human Research Protections (OHRP). We urge FDA and OHRP to work together with external stakeholders to address these recommendations.

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## **Provide further guidance to IRBs on clinical trial Web sites.**

The recent growth of Internet-based recruitment strategies warrants renewed attention in guidance. We recommend that FDA and OHRP develop a new section, within current guidance, that specifically address recruitment practices on the Internet. In regard to clinical trial Web sites, we recommend to FDA and OHRP the following:

### **Clarify that risk and benefit information in trial listings is subject to IRB review and approval.**

Current guidance does not require IRB review if the clinical trial listing is limited to the following basic trial information: title, purpose, of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.<sup>28</sup> This is a sound policy that we do not propose to change. However, some Web sites we reviewed provide more than the prescribed basic trial information mentioned in current guidance. In these instances it is unclear to IRBs whether review of the listing is required. Therefore, we recommend FDA and OHRP make it clear that (1) risk and benefit information in a trial listing is subject to IRB review and approval, and (2) sponsors and investigators have the responsibility to obtain that review. The IRB is the most suitable entity to ensure that risk and benefit information is presented in a balanced and fair manner.

### **Require IRB review of any prescreening used for specific trials.**

Prescreening for specific trials use questionnaires to ask potential subjects personal and sensitive health information to determine their eligibility for those trials. Such screening questions should be subject to IRB review and approval. In instances where this information is personally identifiable and stored, FDA and OHRP should call for IRBs to review this type of prescreening to ensure that appropriate steps have been taken to address privacy issues. Guidance should be similar to what is already in place for receptionist scripts that are used at central call centers.

On page 18, we suggest voluntary standards that IRBs may want to consider for privacy policies of clinical trial Web sites that collect personal information.



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## **Facilitate the adoption and use of voluntary standards for clinical trial Web sites.**

FDA and OHRP should exert leadership to foster the development and application of voluntary standards for clinical trial Web sites. Such standards could address various aspects of these sites, such as accuracy, comprehensiveness and functionality. On the basis of our inquiry, we have developed a preliminary framework offering four standards that are especially pertinent to the role of Web sites in fostering informed consent (see page 18). Developing such standards can be an important way of conveying the important role that Web sites can play as mechanisms of informed consent and of raising the bar of current practice. The standards we propose go beyond the risk-benefit and prescreening information for which we call for mandatory IRB review.

We suggest that FDA and OHRP determine the best ways in which they might exert such leadership to facilitate the development and encourage the use of voluntary standards. Developing such standards would necessitate a broad public dialogue. Our preliminary framework is presented with the intent to help focus discussions on how the Web sites can serve as more significant vehicles of informed consent.<sup>29</sup> One promising approach to facilitate discussion would be to promote public workshops involving key stakeholders such as representatives of Web sites, the broader research community (government and industry), and patient advocacy organizations. FDA and OHRP could propose points to be considered in these workshops.

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## **Encourage clinical trial Web sites to undergo periodic review by independent bodies.**

The conduct of reviews of individual sites by independent parties can be an important step in enhancing the credibility of clinical trial Web sites. Such reviews could address the general information provided on the sites — an area that currently is excluded from IRB review. They could, for example, address privacy policies and procedures to ensure that personal information is handled appropriately. These independent reviews could also address trial-specific information, perhaps involving an examination of a sample of listings to make sure that they provide balanced information about the trials.

Such independent reviews could be performed by IRBs. On their own initiative, two of the Web sites we reviewed have already contracted with IRBs to provide such reviews. The reviews could also be performed by an accrediting body. Although not directly geared toward human-subject protection issues, several organizations already exist that have developed standards for health information Web sites. Four of the Web sites we reviewed are members of the Health on the Net Foundation and subscribe to its eight principles (see appendix C for a description of these organizations).

## Standards for Clinical Trial Web Sites: A Preliminary Framework

Standards		Elements
<b>General Clinical Trial Information</b>	<p><i>Provide a comprehensive overview of clinical trials</i></p> <p>The more subjects know about the process in general the more informed their decision to enroll will be.</p>	<p>A comprehensive overview includes:</p> <ul style="list-style-type: none"> <li>▶ Clear statement that a clinical trial is research not treatment</li> <li>▶ Description of FDA's drug approval process</li> <li>▶ Description of the Common Rule and FDA Good Clinical Practice regulations</li> <li>▶ Description of the informed consent process</li> <li>▶ Description of the role of IRBs</li> <li>▶ Explanation of the importance of weighing risks and benefits</li> <li>▶ Information on how to contact key Federal agencies for further clinical trial information</li> <li>▶ Sources of clinical trial information</li> <li>▶ Explanation of the importance of considering alternatives to a clinical trial.</li> </ul>
	<p><i>Disclose prominently a comprehensive privacy/confidentiality policy</i></p> <p>Disclosure gives consumers control over their personal information before they share it. Consumers should be fully aware of how their personal information will be used.</p>	<p>A comprehensive policy contains the following with regards to personally identifiable information:</p> <ul style="list-style-type: none"> <li>▶ How long is personal information retained</li> <li>▶ What information is collected</li> <li>▶ How information will be used</li> <li>▶ What entities or individuals have access</li> <li>▶ How consumers can eliminate personally identifiable information</li> <li>▶ When the policy was last updated</li> </ul>
	<p><i>Disclose prominently significant financial relationships</i></p> <p>Informs the subject of potential conflicts of interest the Web site may have.</p>	<p>Significant financial relationships include:</p> <ul style="list-style-type: none"> <li>▶ Revenues collected based on Web site services</li> <li>▶ Funding the site receives from pharmaceutical companies, health insurers, trial sites, etc.</li> <li>▶ Agreements for advertising on the site</li> </ul>
<b>Trial-Specific Information</b>	<p><i>Provide key information in clinical trial listings</i></p> <p>Key information about specific trials helps the subject more quickly identify appropriate trials.</p>	<p>Key trial information includes:</p> <ul style="list-style-type: none"> <li>▶ Title</li> <li>▶ Phase</li> <li>▶ Purpose</li> <li>▶ Description of trial</li> <li>▶ Eligibility criteria</li> <li>▶ Duration of trial</li> <li>▶ Time commitment for the subject</li> <li>▶ Balanced description of risks and benefits</li> <li>▶ Compensation for injury</li> <li>▶ Name of trial sponsor(s)</li> <li>▶ Name of clinical investigator(s)</li> <li>▶ Contact information for research site(s) - contact name, phone number, and location</li> </ul>
<b>SOURCE:</b> Office of Inspector General.		

# COMMENTS ON THE DRAFT REPORT

We received comments on our draft report from the Food and Drug Administration, the Office for Human Research Protections, and the National Institutes of Health. Below, we summarize the major comments and, in italics, offer our response. We made a number of changes in the final report, mostly technical in nature. The full text of each set of comments appears in Appendix E.

## Food and Drug Administration

FDA commended our report and indicated it will work to include our recommendations as it reviews its Information Sheets for IRBs and Clinical Investigators. However, FDA expressed concern about the potential burdens to the already overburdened IRBs. As a way of easing the burden, it suggested that Federal guidance might call for IRBs to limit their reviews of trial-specific information to that information not considered basic trial information.

*We modified our recommendations to focus IRB review and approval to the risk and benefit information and prescreening questions for trial listings.*

## Office for Human Research Protections

The Office for Human Research Protections describes the report as “comprehensive and insightful.” But it takes the position that clinical trial Web sites have not only the potential, but also the requirement, to foster informed consent and to meet all provisions of the Federal Common Rule. Even basic trial information, it states, is subject to IRB review. If further guidance is needed to make this clear, it urges it that it be issued.

*OHRP’s response focuses on institutional Web sites that function under the federal assurance process overseen by OHRP. Our review included these sites but also many others that are not part of an institutional assurance. We suggest that FDA and OHRP work together to produce a common set of expectations for all Web sites. The preliminary standards we propose may be helpful in this regard.*

## National Institutes of Health

The National Institutes of Health indicated that it was pleased with the report and offered a number of technical clarifications which we addressed in the report. Substantively, NIH was not clear if IRB approval of a clinical trial listing at the study site was sufficient or if a separate Web approval is needed.

*We have added a clarification in our text that sponsors and investigators are responsible for obtaining IRB approval for any clinical trial Web site listing they initiate that goes beyond providing basic clinical trial information.*

## **The Main Players in Clinical Research**

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Clinical trials for new drugs are complex and require the engagement of many different entities. In recent years, the number of these entities and their agents has proliferated. Below, we describe the roles of and interactions among these players.

### **Sponsors**

Sponsors are the primary agents responsible for conducting the clinical trial and typically are the primary source of funding for the trial. They can be either pharmaceutical companies or Federal agencies such as the National Institutes of Health. Sponsors are responsible for conducting on-site oversight of their trials. This oversight is carried out by monitors. Recently, in an attempt to reduce their research and development costs and to streamline processes, sponsors have started outsourcing many aspects of clinical trials to other entities. Sponsors often delegate a variety of specialized functions, such as the organization and management of clinical trials, to contract research organizations (CROs) which sometimes, in turn, outsource to other specialized entities. Patient recruitment firms, which are public relation firms whose sole mission is recruiting human subjects, have emerged in recent years in response to sponsors' desire for speedy recruitment of subjects.

### **Investigators**

Sponsors depend upon clinical investigators to actually conduct clinical trials. Investigators often rely on their staff to handle the administrative and sometimes much of the clinical work associated with clinical trials. Often, investigators will have a point person, or study coordinator who is a practitioner (generally a nurse) with the primary responsibility to facilitate the conduct of clinical trials. Coordinators may be involved in recruiting and obtaining consent from subjects, as well as maintaining the data for the trial. Investigators conduct trials in a variety of different settings. Traditionally, they have conducted clinical trials primarily in university hospitals, or academic medical centers. Increasingly, research occurs in physicians' private practices or in dedicated research sites, sites exclusively used for research. Some investigators and/or sites have tried to accommodate sponsors' desire for efficient, streamlined trial conduct by forming site networks, sometimes referred to as site management organizations (SMOs).

### **Human Subjects**

The final, and most critical, players in a clinical trial are the human subjects themselves. Subjects may be recruited by an assortment of agents and/or entities: sponsors, contract research organizations, clinical investigators, research coordinators, and patient recruitment firms. In general, sponsors use healthy subjects to test the safety of a drug in first-in-human trials (phase 1 trials). They use subjects with the condition they are targeting to test the efficacy of a drug in later-stage trials (phase 2 and 3 trials).

## Best Practices of Clinical Trial Web Sites

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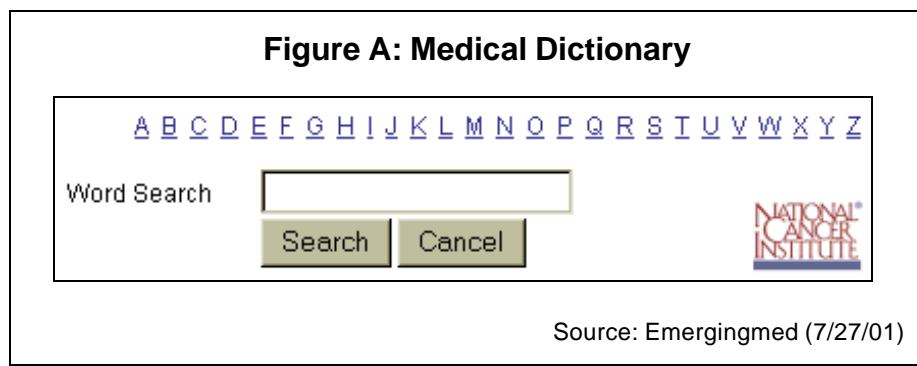
Here, we cite examples from Web sites that best demonstrate the potential for informing individuals about clinical trials.

### Providing General Clinical Trial Information

Partnering with other health content providers can be an important way to further inform people about clinical trials and new medical therapies. Acurian has partnered with HopkinsHealth to provide current disease information. HopkinsHealth is managed by Johns Hopkins Medical Institutions, which disseminates consumer health information on various disease topics that are written by health care professionals.<sup>30</sup> Thus, an individual on Acurian is able to read about the latest news on treatment approaches, preventive health care, and drugs in development.<sup>31</sup>

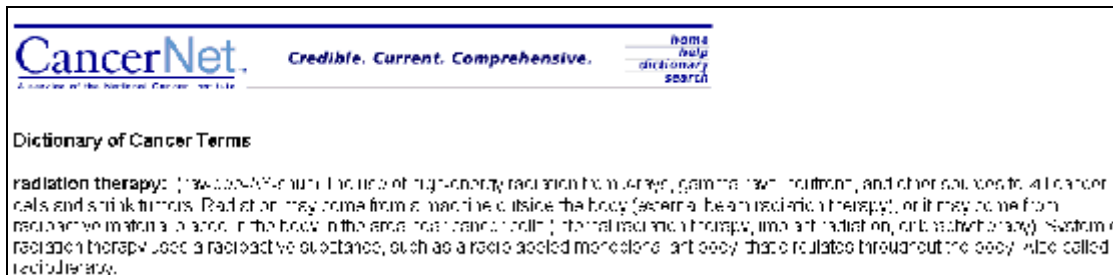
### Defining Key Terms

Some Web sites provide a glossary of terms for technical words an individual may commonly come across while researching clinical trials. CenterWatch and thehealthexchange both provide a comprehensive glossary of clinical research terms in their overview of clinical trials.<sup>32,33</sup> For example, the glossary explains the Declaration of Helsinki, the Common Rule, and adverse events. Instead of providing the glossary in only one location, Emergingmed's "medical dictionary" is accessible from every one of its Web pages (figure A).<sup>34</sup> The site integrates the National Cancer Institute's online dictionary to define multiple cancer terms. This is not only convenient to users, but it also fosters a better understanding of diseases and clinical trials.



CancerNet provides an interactive trial description that links to a glossary. Within each trial listing, selected words are underlined that are active links to the National Cancer Institute’s dictionary of cancer terms (figure B).

**Figure B: Dictionary of Disease Terms**



**Providing Disease Information**

When individuals focus their trial search to one disease, clinical trial Web sites often provide disease-specific information. Each disease category on EmergingMed not only provides clinical trial information, but also standard disease treatments and therapies in development (figure C).<sup>35</sup>

Veritas Medicine provides similar disease information, but, in addition, prominently discloses the names of the physicians who write the information and offers a link that provides their professional background and credentials. Each disease category on Veritas Medicine is developed by one of their medical directors, who are physician-scientists with an expertise in a particular disease category.<sup>36</sup> They provide information about disease and

**Figure C: Disease Information**



Source: Emergingmed (7/28/01)

standard treatment and investigational treatments within their disease category. This places accountability on the Web site and fosters confidence that the information provided is accurate and reliable (figure D).<sup>37</sup>

ClinicalTrials.gov offers specific disease information by providing links to MEDLINEplus related topics. MEDLINEplus is a repository of health information from the National Library of Medicine.<sup>38</sup> This service provides access to extensive medical information about specific diseases and conditions.

**Figure D: Source of Information**

**Diabetes**

The information in this section is written by:  
Evan D. Rosen, M.D., Ph.D. [read bio](#)  
Instructor in Medicine, Harvard Medical School

Source: Veritasmedicine (7/28/01)

**Providing Drug Information**

For drugs involved in AIDS clinical trials that are listed on the National Institute of Allergy and Infectious Disease database, actis.org, the site provides links to the AIDS DRUGS Database. In the trial description, an individual “clicks” on the underlined drug name and is automatically linked to extensive AIDS drug information (figure E).<sup>39</sup> Drug descriptions include links to relevant articles on PubMed and to current and past trials that have used the drug.

**Figure E: Drug Information**

**Drugs Used in this Trial**

Generic/Code Name  
Zalcitabine  
Generic/Code Name  
Zalcitabine  
Generic/Code Name  
Zalcitabine  
Generic/Code Name  
Zalcitabine

Source: ACTIS (7/28/01)

**Describing Systems for Protecting Human Subjects**

Educating individuals about the protections of human subjects in clinical trials is an important part of the trial process that fosters informed consent. An explanation of human-subject protections includes describing the drug approval process, informed consent and the role of IRBs. In their overview of clinical trials, CenterWatch summarizes the protection of human subjects through IRB approval and the informed consent process (figure F on following page).

**Figure F: Description of Protections for Human Subjects**

The patient's rights and safety are protected in two important ways. First, any physician awarded a research grant by a pharmaceutical company or the NIH must obtain approval to conduct the study from an Institutional Review Board. The review board, which is usually composed of physicians and lay people, is charged with examining the study's protocol to ensure that the patient's rights are protected, and that the study does not present an undue or unnecessary risk to the patient. Second, anyone participating in a clinical trial in the United States is required to sign an "informed consent" form. This form details the nature of the study, the risks involved, and what may happen to a patient in the study. The informed consent tells patients that they have a right to leave the study at any time.

Source: CenterWatch (4/10/01)

CancerTrials, an arm of CancerNet, offers a comprehensive description in a section entirely devoted to the "Protections for Participants in Clinical Trials".<sup>40</sup> This section gives simple explanations and links to safeguards the government has in place to protect human subjects such as the informed consent process and larger systems of Federal protection like the Common Rule and the Office for Human Research Protections.<sup>41</sup>

**Explaining Risks**

Of the Web sites we reviewed, only the National Cancer Institute's CancerNet Web site provides a general discussion in the trial listing about the possible risks associated with participating in a cancer trial. Each trial description contains the following explanation that addresses therapeutic misconceptions individuals may have about participating in a cancer trial (figure G on following page).



### Figure G: Explanation of Risks

#### Warning

The purpose of most clinical trials listed in this database is to test new cancer treatments, or new methods of diagnosing, screening for or preventing cancer. Because all potentially harmful side effects are not known before a trial is conducted, dose and schedule modifications may be required for participants if they develop side effects from the treatment or test. The therapy or test described in this clinical trial is intended for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this clinical trial should be consulted before

### Providing Additional Assistance

**One-on-one assistance.** Individuals who need assistance in searching for clinical trials on CancerNet have access to live online assistance from an informational specialist, who will answer questions about how to use and navigate the Web site. Assistance is available in the afternoons five days a week (figure H).<sup>42</sup>

Other Web sites may offer a toll-free number to lend assistance for navigating through their site or registering for a trial. Veritas Medicine offers assistance eight hours a day, five days a week.<sup>43</sup>

### Figure H: Online Assistance

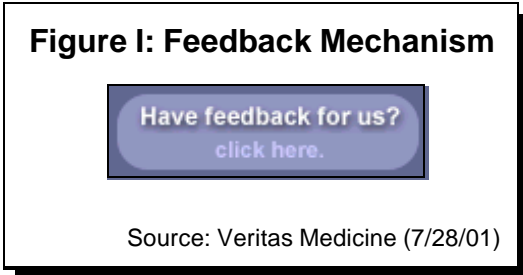
Need help finding information?  
 Chat online with the NCI  
 Available M-F, 12-4 pm ET



cancer.gov

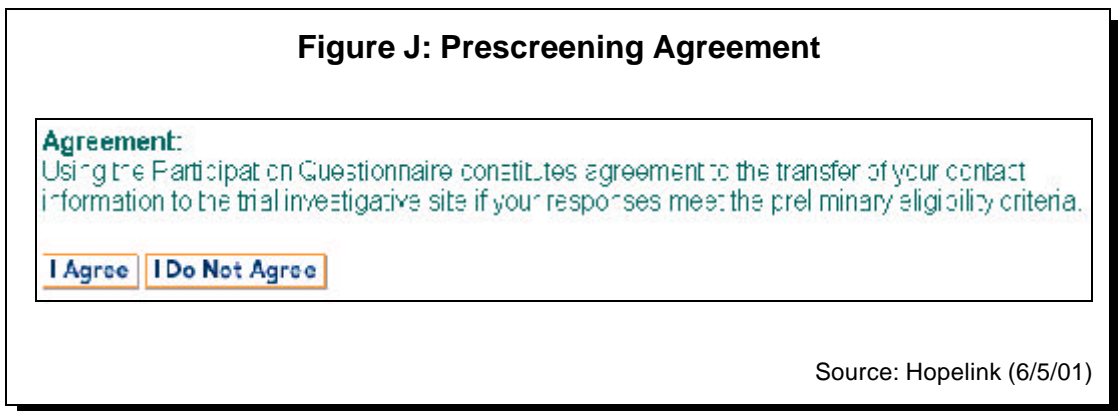
Source: CancerTrials (6/16/01)

A feedback mechanism is useful to let sites know whether they are providing their consumers with the services they want. Feedback also allows an individual to tell the site what services are lacking and what needs improvement. Veritas Medicine provides an online feedback form and will also respond to comments when an e-mail address is provided (figure I).



### **Safeguarding Personal Information During Prescreening**

Recruitment Web site privacy policies are particularly important to the consumer when the site provides a prescreening service and collects personal health information. Two Web sites we reviewed automatically display a window that discloses to the consumer their intent to collect personal health information through a questionnaire. At the end of a trial description, for those trials that offer the option to prescreen online, Hopelink provides a “Participation Questionnaire”. Prior to the questionnaire, Hopelink provides a web page that describes the purpose and process of the questionnaire. In order to proceed to the questionnaire, individuals must agree to transfer their contact information to the trial investigative site and click “Agree” (figure J is a portion of the prescreening agreement).



## Health Internet Organizations

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The organizations below represent the self-regulatory efforts of the Internet health industry to provide credible and reliable health information to consumers. Membership is open to all Web sites that provide health information.

### Health on the Net Foundation

The Health on the Net Foundation (HON) is an international initiative whose mission is to “guide lay persons or non-medical users and medical practitioners to useful and reliable online medical and health information”. In 1996, the Foundation established a code of conduct, the HONcode, that consists of eight principles of reliable health information on the Internet. Membership is free. A Web site fills out a questionnaire to verify that it follows HONcode principles and, if not, the steps it will take to comply. The Web site then receives the HTML code for the seal to post on the Web site. Below are the eight principles.<sup>44</sup>



1. *Authority.* Any medical or health advice provided and hosted on this site will only be given by medically trained and qualified professionals unless a clear statement is made that a piece of advice offered is from a non-medically qualified individual or organization.
2. *Complementarity.* The information provided on this site is designed to support, not replace, the relationship that exists between a patient/site visitor and his/her existing physician.
3. *Confidentiality.* Confidentiality of data relating to individual patients and visitors to a medical/health Web site, including their identity, is respected by this Web site. The Web site owners undertake to honor or exceed the legal requirements of medical/health information privacy that apply in the country and state where the Web site and mirror sites are located.
4. *Attribution.* Where appropriate, information contained on this site will be supported by clear references to source data and, where possible, have specific HTML links to that data. The date when a clinical page was last modified will be clearly displayed (e.g. at the bottom of the page).
5. *Justifiability.* Any claims relating to the benefits/performance of a specific treatment, commercial product or service will be supported by appropriate, balanced evidence in the manner outlined above in Principle 4.

6. *Transparency of authorship.* The designers of this Web site will seek to provide information in the clearest possible manner and provide contact addresses for visitors that seek further information or support. The Webmaster will display his/her E-mail address clearly throughout the Web site.
  
7. *Transparency of sponsorship.* Support for this Web site will be clearly identified, including the identities of commercial and non-commercial organizations that have contributed funding, services or material for the site.
  
8. *Honesty in advertising & editorial policy.* If advertising is a source of funding it will be clearly stated. A brief description of the advertising policy adopted by the Web site owners will be displayed on the site. Advertising and other promotional material will be presented to viewers in a manner and context that facilitates differentiation between it and the original material created by the institution operating the site.

## **Hi-Ethics**

Hi-Ethics is a consortium of several health Web sites. The goal of the organization is “to earn the consumer's trust and confidence in Internet health services”. Web sites pay an annual fee for membership. Hi-Ethics is developing a new program with TRUSTe (see next description) due out in 2001. Hi-Ethics established 14 ethical standards to ensure Web sites provide reliable and current health information and safeguard confidentiality and security of personal information. Below is a brief description of each of the 14 standards.<sup>45</sup>

- |   |   |
|---|---|
| <ol style="list-style-type: none"> <li>1. Privacy Policies- Disclose use of aggregate and personal health information.</li> <br/> <li>2. Enhanced Privacy Protection for Health-Related Personal Information- Disclose use of personal health information.</li> <br/> <li>3. Safeguarding Consumer Privacy in Relationships with Third Parties- Disclose third party use and access to person health information.</li> <br/> <li>4. Disclosure of Ownership and Financial Sponsorship- Disclose major financial interests in the Web site or its partners.</li> </ol> | <ol style="list-style-type: none"> <li>5. Identifying Advertising and Health Information Content Sponsored by Third Parties- Disclose how the Web site accepts advertising and obtains health information, clearly distinguish advertising from health information, and disclose significant relationships between commercial sponsors and health content.</li> <br/> <li>6. Promotional Offer, Rebates, and Free Items or Services- Will comply with Federal and state laws regarding these services offered by the Web site</li> <br/> <li>7. Quality of Health Information Content- The Web site will not provide false or misleading health information or advertising</li> </ol> |
|---|---|

**8. Authorship-** Disclose source of health information and provide a conflict of interest policy for all authors. Any information created by the Web site will disclose the date it was created or last updated.

**9. Disclosure of Source and Validation for Self-Assessment Tools-** Disclose the source and scientific basis for their use.

**10. Professionalism-** Maintain and adhere to professional ethical principles.

**11. Qualifications-** Provide credentials and qualifications of those persons supplying health information to the Web site and disclose if the information is verified.

**12. Transparency of Interactions, Candor and Trustworthiness-** Inform consumers of the risks, responsibilities, and reasonable expectations associated with using the Web site. The Web site will make apparent to consumers when they are moving from one site to another that may involve a change in the assumed risks, responsibilities, and expectations of the site.

**13. Disclosure of Limitations-** Disclose the limitations of the health information provided on the Web site and emphasize that the services provided are not intended to take the place of the health professional-patient relationship.

**14. Mechanism for Consumer Feedback-** Make it easy for consumers to provide feedback or complaints.

## **TRUSTe**

TRUSTe is an online privacy seal program that assures consumers that Web site members adhere to their privacy principles. All Web sites that display the seal must disclose their personal information collection and privacy practices. Disclosure gives Internet users assurance of privacy and choice over how their personal information is collected, used, and shared by Web sites.<sup>46</sup>



## **Utilization Review Accreditation Commission (URAC)**

URAC, is an organization that has created a health Web site accreditation program. In collaboration with Hi-Ethics, URAC's accreditation program incorporates the 14 Hi-Ethics standards. Accredited members display the URAC seal on their site. Accreditation includes a fee, an initial audit, and random inspections.<sup>47</sup> The final standards were approved by URAC on July 27, 2001.

## Internet Healthcare Coalition

The Internet Healthcare Coalition aims to promote ethical principles within the Internet health industry. The coalition is comprised of representatives from the industry, government, medicine, law, and patient and consumer groups. In May 2000, the coalition released the final draft of their code of ethics meant to be used by Web sites providing health information. The code addresses eight principles.<sup>48</sup>

1. Disclose information that if known by consumers would likely affect consumers' understanding or use of the site or purchase or use of a product or service.
2. Be truthful and not deceptive.
3. Provide health information that is accurate, easy to understand, and up to date. Also, provide the information users need to make their own judgments about the health information, products, or services provided by the site.
4. Respect users' right to determine whether or how their personal data may be collected, used, or shared.
5. Respect the obligation to protect users' privacy.
6. Respect fundamental ethical obligations to patients and clients. Also, inform and educate patients and clients about the limitations of online health care.
7. Ensure that organizations and Web sites with which they affiliate are trustworthy.
8. Provide meaningful opportunity for users to give feedback to the site. Also, Web sites will monitor their compliance with the *eHealth Code of Ethics*.

**Summary Data of Web Site Review**

The table below presents all the 22 Web sites contained in our review.

<b>Table 1: The 22 Web Sites Reviewed</b>	
Federal Web Sites	<ul style="list-style-type: none"> <li>▶ actis.org</li> <li>▶ cancernet.nci.nih.gov</li> <li>▶ clinicaltrials.gov</li> </ul>
Third-Party Web Sites	<ul style="list-style-type: none"> <li>▶ acurian.com</li> <li>▶ americasdoctor.com</li> <li>▶ centerwatch.com</li> <li>▶ clinicaltrials.com</li> <li>▶ drugmonitor.com*</li> <li>▶ drugstudycentral.com</li> <li>▶ emergingmed.com</li> <li>▶ trialpages.com</li> <li>▶ veritasmedicine.com</li> <li>▶ thehealthexchange.org</li> <li>▶ hopelink.com</li> <li>▶ mycure.com</li> </ul>
Location-Specific Web Sites	<ul style="list-style-type: none"> <li>▶ clinicaltrials.iupi.edu</li> <li>▶ crnet.mgh.harvard.edu</li> <li>▶ mayo.edu/research/clinical_trials.html</li> <li>▶ med.umich.edu/gcrc</li> </ul>
Sponsor-Specific Web Sites	<ul style="list-style-type: none"> <li>▶ amgentrials.com</li> <li>▶ icsltd.net/clinicalstudies</li> <li>▶ glaxowellcome.com/clinicaltrials_external/clinicaltrials.html</li> </ul>
<p>*drugMonitor.com is no longer in operation. Source: OIG Data Analysis</p>	

**APPENDIX D**

The table below represents elements used to score each of the 22 Web sites.

<b>Table 2: Review of 22 Clinical trial Web sites</b>			
<b>General Element</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>
Offers a membership service	13	9	0
Membership required in order to search for trials	1	11	10
Membership required in order to obtain contact information	6	6	10
Describes FDA's drug approval process	12	10	0
Describes the Common Rule	2	20	0
Describes the role of IRBs	16	6	0
Describes the informed consent process	21	1	0
Discusses the importance of weighing the risks and benefits	12	10	0
Provides links to Federal Web sites for more information	14	8	0
Provides a clear statement that clinical trials are research, not treatment	16	6	0
Discloses payments it receives	6	6	10
Discloses who is responsible for content	3	19	0
Accepts advertisements	3	19	0
Discloses its policy for advertisements	3	19	0
Member of e-ethics organization	4	18	0
Provides an online privacy policy	17	5	0
Collects personally identifiable information	13	9	0
Discloses how long personally identifiable information is retained	2	11	9
Discloses that personally identifiable information can be deleted or edited	8	5	9
Discloses the processes it has in place to secure provided info in transit	4	9	9
Discloses it policy to notify users of changes in its privacy policy	5	8	9
Source: OIG Data Analysis			



**APPENDIX D**

The table below represents elements used to score each of the five specific clinical trials on each of the 22 Web sites, for a total of 110 clinical trials.

<b>Trial Specific Elements</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>
Provides a title for the trial	58	52	0
Indicates the phase of the trial	38	69	3
Indicates the purpose of the trial	80	30	0
Provides eligibility criteria	91	19	0
Provides a general description of the protocol	54	56	0
Indicates the time commitment required	48	62	0
Describes of risks associated with trial	0	110	0
Describes of benefits associated with trial	29	81	0
Provides sponsor's name	23	77	10
Provides investigator's name	47	63	0
Provides contact information at the trial site	84	6	20
Provides disease treatment information	11	99	0
Source: OIG Data Analysis			



DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Date: February 14, 2002

From: Acting Principal Deputy Commissioner

Subject: OIG Draft Report: "Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent," OEI-01-97-00198

To: Inspector General

I want to commend the Office of the Inspector General for this thoughtful and informative report. The report's four proposed standards for clinical trial Web sites should be helpful to entities developing or operating these sites.

We have reviewed your recommendations, including the following:

- (1) Provide further guidance to IRBs on clinical trial Web sites.
- (2) Facilitate the adoption and use of voluntary standards for clinical trial Web sites.
- (3) Encourage clinical trial Web sites to undergo periodic review by independent bodies.

FDA is reviewing and revising the Agency's Information Sheets for IRBs and Clinical Investigators and will work to include the OIG's recommendations during this process. FDA will also work to ensure that guidance in this area is consistent between FDA and the Office of Human Research Protections (OHRP).

We are concerned by the recommendation that an IRB should review trial listings that go beyond basic trial information. The report identifies "key trial information" as including a "balanced description of risks and benefits." Yet the report recommends IRB review if trial-specific information about risks or benefits is included in the listing. This could significantly increase the workloads of already burdened IRBs. If Federal guidance required IRB review of all clinical trial listings containing descriptions of risks and benefits, it is likely this key information will not be included.

It may be less burdensome, while providing equivalent protection, to require only review of that information not considered basic trial information in current Federal guidance. For example, if a clinical trial listing were to contain a description of risks and benefits, IRB review of that risk/benefit description, rather than the entire clinical trial listing, could be required. It is not clear from the report whether this interpretation would meet the spirit of the report's recommendation.

Page 2 – Inspector General

FDA will meet with OHRP to discuss potential forums for discussing the adoption and use of voluntary standards for clinical trial Web sites, as the report recommends. FDA will also use such forums and other venues to relay the OIG's recommendation to encourage the periodic review of clinical trial Web sites by independent bodies. FDA further proposes to discuss this recommendation with the IRB community and with any accrediting bodies engaged in FDA-regulated review.

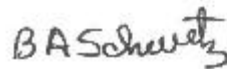
We also offer the following technical comments:

Page iv and page 18: The third element associated with the first standard ("Provide a comprehensive overview of clinical trials") should reference FDA regulations as well as the Common Rule: i.e., "Description of the Common Rule and FDA Good Clinical Practice regulations"

Appendix C, Hi-Ethics ethical standards: Standard 13 (Disclosure of Limitations): Replace "provide" with "provided" in the clause "...the services provide are not intended to take the place..."

Appendix E, Endnote #5, final sentence: Replace "financial" with "financially" in the phrase "...providing the information financial benefits from subjects that actually enroll."

We appreciate the work that went into this very informative report.



Bernard A. Schwetz, D.V.M., Ph.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Public Health and Science

Greg Koski, Ph.D., M.D., Director  
Office for Human Research Protections  
The Tower Building  
1101 Wootton Parkway, Suite 200  
Rockville Maryland 20852

TO: Janet Rehnquist  
Inspector General

FROM: Director, Office for Human Research Protections

SUBJECT: OIG Draft Report: "Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent," OEI-01-97-00198

Thank you for the opportunity to review the draft Report produced by your office on the development and use of clinical trial web sites and the role of institutional review boards (IRBs) in overseeing the information on these web sites.

The centerpiece in protecting human research subjects is the clear communication of information, the activity which initiates the informed consent process. The rapid expansion in the number of web sites devoted to clinical trial information, and the additional evolution of their role to human subject recruitment, has both increased the opportunities to effectively communicate with participants in clinical research, and has also increased the need for IRBs to be vigilant in assuring that the rights of the subject-participants in making informed decisions are protected.

This responsibility is even more greatly felt with knowledge of the data your team has uncovered about failures of these sites to adequately transmit information, activities that also directly relate to requirements of the Common Rule for Protection of Human Subjects. The Office for Human Research Protections (OHRP) seriously regards and will continue providing guidance to IRBs concerning their review of trial listings on the web that go beyond basic and general public information. We also agree that encouragement of voluntary standards for these sites should be highlighted in OHRP workshops and other forms of communication.

A review of the draft report is attached.

Greg Koski, M.D., Ph.D.

Attachment

## Review

## Office of Inspector General Draft Report:

Clinical Trial Web Sites—A Promising Tool to Foster Informed Consent

Clinical trial web sites were first established several years ago to provide general information about what new medical interventions were being studied in clinical settings at institutions around the world. Some were specific to institutions and others began to attempt cataloging all known clinical trials by disorder, intervention type or agent, and institution. Sponsors, investigators, and patient groups soon realized that the sites afforded an opportunity to inform potential subjects with specific disorders about relevant clinical trials and, further, to outline protocol requirements with an intent to recruit subjects for those trials.

The Report is both comprehensive and insightful in describing this information sharing process. However, the Report approaches the topic from the viewpoint that web sites which intend to recruit human subjects have only the potential, but not the requirement, for fostering informed consent. In fact, it is the position of the Office for Human Research Protections (OHRP) that when an institution that is intent upon recruiting human subjects for a research program begins providing information to web site readers for the purpose of recruitment, the process of informed consent has already begun, and requirements of the Common Rule for Protection of Human Subjects ("Common Rule") must be taken into account. OHRP's position would be that even basic information on trial-specific web listings intended to be seen by prospective human subjects is subject to IRB review and approval under the Common Rule whenever the clinical trial is federally supported or conducted.

If it is perceived that Federal guidance for IRBs fails to make clear when such provision of information to human subjects is addressed by the Common Rule and requires IRB review, further guidance, as recommended by the Report, is essential. OHRP would further recommend that, to assist in this process, the Report reference the scope and specific requirements of the Common Rule throughout the document and provide reference links to the regulations that apply to research that is within the oversight jurisdiction of DHHS and FDA.

The information contained in Appendix B of the Report is excellent, giving the reader specific examples of best practices for such web sites. OHRP agrees that such information and the encouragement of voluntary standards would be a valuable part of workshops and other means of communication.



DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

National Institutes of Health  
Bethesda, Maryland 20892  
www.nih.gov

**TO:** Janet Rehnquist  
Inspector General, HHS

**FROM:** Acting Director, NIH

**SUBJECT:** NIH Comments on the Office of Inspector General (OIG) Draft Report:  
"Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent"  
(OEI-01-9700198)

We appreciate the opportunity for the National Institutes of Health (NIH) to comment on the draft OIG report on clinical trial web sites. In general, we are very pleased with the report; and, in particular, that it is complimentary of the National Cancer Institute's Web site.

I have attached comments from several NIH Institutes and the Office of Extramural Research concerning parts of the report that we would like you to consider changing. Should you or your staff have any questions, please have them call Mary Jane Meyers, Office of Management Assessment, Division of Outside Review and Liaison, NIH, at (301) 402-8482.

Thank you again for the opportunity to comment.

Ruth L. Kirschstein, M.D.

Attachment

**NIH Comments on OIG Draft Report:  
"Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent"  
(OEI-01-97-00198)**

1. The data for the numbers of visitors that are attributed to CancerTrials on page i of the Executive Summary and page 5 of the report should actually be attributed to CancerNet.
2. Page iii - On this page and in other places in the document, it is not clear if an institutional IRB (Institutional Review Board) approval at the study site is sufficient or if a Web IRB approval is also being recommended. It would seem, if no information were changed, that the institutional IRB approval would be all that is needed.
3. Page iii - In addition to IRB approval of sites, there should be other recommendations made for the periodic reviews, such as editorial board reviews done by outside participants.
4. Page 9 - The example used in Figure C may not be the best one to make the point since it discusses a Phase I trial that has effectiveness as an endpoint; it is using standard therapies in a novel way. Since you discuss Phase I in other places in the document as toxicity studies (see page 11), this could be confusing to the reader.
5. Page 11 - Please be aware that when discussing Phase I studies, at least in cancer, these studies may not be "first time in humans" (example #3) but can also be evaluations of a new dosage or new mode of administration.

1/31/02

## Endnotes

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1. Diana L. Anderson, *A Guide to Patient Recruitment* (Massachusetts: CenterWatch, 2001), 25.
2. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (Washington, D.C.: U.S. Government Printing Office, 1978) DHEW Publication No. (OS) 78-0012. Reprinted in *Federal Register* 44 (April 18, 1979):23192.
3. We mention these concerns in two prior reports: (1) U.S. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193, June 1998 and (2) U.S. Department of Health and Human Services, Office of Inspector General, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* (OEI-01-97-00195), June 2000.
4. 21 CFR § 50 & 56 and 45 CFR § 46.
5. We recognize that some Web sites view themselves as educational resources rather than recruitment vehicles. We believe this reflects a limited view of recruitment. Any information that is provided to subjects with the intent of informing them about specific clinical trials that are actively enrolling is recruitment. Recruitment is not contingent on whether or not the entity providing the information financially benefits from subjects that actually enroll.
6. ClinicalTrials.gov was developed as a result of the FDA Modernization Act on 1997. Section 113 requires Department of Health and Human Services, through NIH, to establish a registry of clinical trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases or conditions. *About ClinicalTrials.gov*; [ <http://www.clinicaltrials.gov>, accessed April 19, 2001]. Available to industry are guidance documents entitled “Information Program on Clinical Trials for Serious or Life-Threatening Diseases or Conditions”, which provide information to industry on the submission of protocol information to the clinical trials databank. 67 Fed. Reg. (No.52), 18 March 2002.
7. “Total visitors” includes the number of unique visitors and repeat visitors.
8. Diana L. Anderson, *A Guide to Patient Recruitment* (Massachusetts: CenterWatch, 2001), 25.
9. A “user session” is the period from which a individual enters and browses a Web site to the time the individual leaves the site.



10. Diana L. Anderson, *A Guide to Patient Recruitment* (Massachusetts: CenterWatch, 2001), 177.
11. Ken Getz, "Patient Experience in Industry-Sponsored Clinical Trials," presented at the Institute of Medicine's Clinical Research Roundtable, September 2000, Washington, DC.  
[<http://www4.nationalacademies.org/IOM/iomhome.nsf/18ace18eb695f74c85256691007102f5/583d8f1384e9e858852569bc00511d59?OpenDocument>, downloaded on June 20, 2001].
12. "New Data Show Internet Website and Email Usage by Physicians All Increasing," *Harris Interactive*. Volume 1 (February 26, 2001) Issue 8.
13. "More online, doing more," The Pew Internet Project: Internet Tracking Report, February 18, 2001; [[http://www.pewtrusts.com/pdf/vf\\_pew\\_internet\\_population\\_report.pdf](http://www.pewtrusts.com/pdf/vf_pew_internet_population_report.pdf), accessed on July 17, 2001].
14. Ibid.
15. [http://www.clinicaltrials.gov/ct/gui/c/w2b/screen/BrowseAny?recruiting=true&path=%2Fbrowse%2Fby-condition%2Fhier&JServSessionIdzone\\_ct=zwrpyg7n71](http://www.clinicaltrials.gov/ct/gui/c/w2b/screen/BrowseAny?recruiting=true&path=%2Fbrowse%2Fby-condition%2Fhier&JServSessionIdzone_ct=zwrpyg7n71), accessed on July 30, 2001.
16. Ibid.
17. Harper, B. and Moench, L. "Emerging Patient Recruitment Performance and Cost Metrics" *Parexels's Pharmaceutical R& D Statistical Sourcebook*, 2000, p. 104.
18. "A Look at Advertising Expenses Per Patient Recruited," *Parexels's Pharmaceutical R& D Statistical Sourcebook*, 2000, p. 103.
19. Diana L. Anderson, *A Guide to Patient Recruitment* (Massachusetts: CenterWatch, 2001), 178.
20. U.S. Department of Health and Human Services, Office of Inspector General, *Recruiting Human Subjects: Pressures in Industry-Sponsored Research*, OEI-01-97-00195, June 2000.
21. <http://www.clinicaltrials.com>, accessed on June 11, 2001.
22. <http://www.drugstudycentral.com>, accessed on June 22, 2001.
23. <http://www.emergingmed.com>, accessed on April 4, 2001.
24. Sponsors and investigators also play a critical role in ensuring human-subject protections but they are also responsible for conducting the research.

25. FDA's Information Sheets. *Guidance for Institutional Review Boards and Clinical Investigators 1998 Update*. <http://www.fda.gov/oc/ohrt/irbs/toc4.html>, accessed on July 17, 2001.
26. In a prior report we found that IRBs are overburdened because workloads have increased while staffing levels and budgets have remained the same. U.S. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193, June 1998.
27. U.S. Department of Health and Human Services, Office of Inspector General, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* (OEI-01-97-00195), June 2000.
28. FDA's Information Sheets. *Recruiting Study Subjects*. September 1998, p.29.
29. In June 2001, FDA issued draft guidance for industry on trial-specific information that should be included in clinical trial listings submitted to ClinicalTrials.gov. FDA and OHRP can use this draft guidance to facilitate discussions for voluntary standards addressing the trial-specific information that should be provided on clinical trial Web sites.
30. [http://www.acurian.com/diseases/bridge\\_features.jsp](http://www.acurian.com/diseases/bridge_features.jsp), accessed on July 17, 2001.
31. A Web site "homepage" is defined as the Web page that is displayed and viewed when a user initially visits a particular site.
32. Accessed on July 27, 2001 at [<http://centerwatch.com/patient/glossary.html>]
33. <http://thehealthexchange.org>, accessed on July 27, 2001.
34. <http://emergingmed.com>, accessed on July 27, 2001.
35. <http://www.emerginmed.com>, accessed on July 28, 2001.
36. [http://www.veritasmedicine.com/fm/about\\_us/about.cfm?mode=5/](http://www.veritasmedicine.com/fm/about_us/about.cfm?mode=5/), accessed on July 28, 2001.
37. [http://www.veritasmedicine.com/d\\_index.cfm](http://www.veritasmedicine.com/d_index.cfm), accessed on July 28, 2001.
38. <http://www.nlm.nih.gov/medlineplus/>, accessed on July 28, 2001.
39. <http://www.actis.org>. Evaluation of an Anti-HIV Drug Combination That Includes a Coated Form of Didanosine (ddI EC) Compared to a Typical Anti-HIV Drug Regimen, accessed on July 28, 2001.

40. <http://cancertrials.nci.nih.gov/understanding/index.html>, accessed on June 7, 2001.
41. <http://cancertrials.nci.nih.gov/understanding/indepth/protections/consent/pt01bgd.htm>, accessed on June 19, 2001.
42. <http://cancertrials.nci.nih.gov/understanding/index.html>, accessed on June 16, 2001.
43. <http://veritasmedicine.com>, accessed on July 28, 2001.
44. More information on the Health on the Net Foundation is available at [www.hon.ch/](http://www.hon.ch/).
45. More information on Hi-Ethics is available at [www.hiethics.com](http://www.hiethics.com).
46. More information about TRUSTe is available at [www.truste.org](http://www.truste.org).
47. More information about URAC is available at [www.urac.org](http://www.urac.org).
48. More information about the Internet Healthcare Coalition is available at [www.ihealthcoalition.org](http://www.ihealthcoalition.org).

# ACKNOWLEDGMENTS

This report was prepared under the direction of Mark. R. Yessian, Ph.D., Regional Inspector General for Evaluation and Inspections in Boston and Joyce M. Greenleaf, M.B.A., Assistant Regional Inspector General. Other principal Office of Evaluation and Inspections staff who contributed include:

China D. Eng, *Program Analyst*

Steven P. Keenan, *Program Analyst*

Aimee K. Golbitz, *Program Analyst*

Genevieve Nowolinski, *Program Specialist*