Disclosure of Information to Potential Subjects on Research Recruitment Web Sites

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Recruitment practices in clinical research may be changing rapidly as use of the Internet grows. Last year, 73% of Americans were reported to be using the Internet.[1] Yet despite the developing influence of the Internet as a tool for reaching potential subjects, few systematic studies have been conducted that explore how individuals are recruited via the Internet for research studies or what type of information clinical trial Web sites provide to prospective research participants.

In 2002, the Department of Health and Human Services' (DHHS) Office of Inspector General (OIG) examined 22 Web sites—federal sites, third-party sites, location-specific sites, sponsor-specific sites, and others—that listed a total of 110 clinical trials. Of these 22 sites, 21 explained the importance of informed consent, and 16 described the role of Institutional Review Boards (IRBs). However, of the 110 trials listed, only 29 mentioned potential research benefits, while none mentioned potential risks. Some Web sites provided misleading information (e.g., referring to "new drug treatments" rather than "experimental" or "unproven drugs"). Of note, this 2002 report did not describe how the particular Web sites within each category were chosen.

Based on its review, the OIG recommended that the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) provide guidance to IRBs concerning clinical trial Web sites; that risk and benefit information be balanced and subject to IRB review; that use of voluntary standards by Web sites be facilitated; and that Web sites be reviewed periodically by independent bodies. Subsequently, in September 2005, the OHRP issued a report, "Guidance on Institutional Review Board Review of Clinical Trial Websites," that stated:

> When information posted on a clinical trial website goes beyond directory listings with basic descriptive information, such information is considered part of the informed consent process and thus requires IRB review and approval. Basic descriptive information includes: study title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information. Information exceeding such basic listing information includes descriptions of clinical trial risks and potential benefits. . . . IRBs should pay particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner. . . . IRBs reviewing clinical trial Web sites also should assess the types of incentives, if any, being offered to prospective subjects. Monetary and non-monetary incentives (e.g., access to services or programs) can create undue influence on a potential subject's decision about participation.[2]

Even before the OHRP issued its guidance, the FDA had provided essentially the same guidance for IRB review of clinical trial Web sites. In 1998, the FDA noted in its document, "Guidance for Institutional Review Boards and Clinical Investigators," that

> IRB review and approval may assure that . . . additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.[3]

The FDA has also pointed out that it "considers direct advertising for study subjects to be the start of the informed consent and subject selection process,"[4] and the OHRP has said that "in some cases, the information provided on these [clinical trial] websites may constitute the earliest components of the informed consent process."[5]

Clearly, this regulatory guidance is important, yet the degree to which trial sponsors, Principal Investigators (PIs), and IRBs follow FDA and OHRP guidance has not been examined. Web sites may provide the first information that a potential research subject sees about a study, and anecdotal information suggests that some individuals decide to enroll in a study before they have even seen the informed consent document or participated in the informed consent process. From a theoretical perspective, Kahneman and Tversky[6] have described an "anchoring heuristic," whereby initial information provided to an individual "anchors" or establishes a mental framework that shapes views and the ways in which information is weighed and may

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affect subsequent decisions. Research has shown that even the order in which risks and benefits are presented can influence perceptions.[7]

Studies have explored potentially related areas: print and Web site advertisements that recruit job applicants; print ads for recruiting research participants; and Web sites for clinical services. For example, job recruitment ads that enhance the physical features of the advertisement (e.g., white space, size, border, and graphics) increase the quantity of applicants.[8] In online job ads, navigational ease may be related to positive impressions.[9] Print ads are often used to recruit research participants,[10] but studies have focused on their cost-effectiveness[11] rather than their mention of risks, benefits, or other key aspects of their content. The American Medical Association (AMA) has issued guidelines for clinical Web sites that provide medical and health information,[12] but these guidelines often are not followed.[13]

Recently, particular controversy has arisen regarding the role of incentives in recruitment for participation in clinical trials, including their appropriateness and influence on the decision whether to enroll. Emanuel has argued that IRBs are too concerned about "undue inducement"[14] as opposed to risk and informed consent. But controversy remains regarding the possibility of undue inducement, and ambiguity continues about how to define undue influence.[15] Few empirical studies have probed what roles payments or other incentives have on potential participants' decisions. Payments vary widely at institutions that compensate research subjects,[16] and amounts of payment may correlate with willingness to participate.[17] But how often protocols in fact compensate participants remains unknown. Hence, the presence of information about incentives on Web sites may be of added interest, as it may help inform these discussions.

In order to learn more about these issues, we examined systematically how a sample of Web sites that recruit participants for research on particular diseases present studies to potential subjects, exploring the presence of information about research benefits, risks, procedures, and incentives, including monetary incentives. Such data can elucidate the degree to which federal guidance is being followed and may have potential implications for policy, suggesting areas that IRBs, policy-makers, and regulators may want to consider further regarding online recruiting of research participants.

Study Methods

To obtain a systematic, diverse sample of research studies, we chose two areas of clinical research—diabetes and depression—since both disorders are fairly common (with United States lifetime prevalence nearly 7% for diabetes[18] and 13% for depression[19]), are much investigated, and involve a range of types of studies and patient populations. We decided to simulate the steps that a prospective research participant might take. Specifically, we conducted online searches with the Google™ search engine, entering the terms "participate in diabetes research study" and "participate in depression research study." We included Web sites that were actively recruiting research subjects. All diabetes sites were included. Of depression sites, we included those for studies of unipolar depression and excluded those for studies of bipolar disorder to allow for more uniformity, given the many differences between these two disorders, and to reduce other potentially confounding variables (e.g., studies of bipolar disorder often involve treatment of both depression and mania). For studies that had one common set of procedures and then additional optional procedures, we included only those parts of the study in which all subjects would participate. For each disease category, we analyzed the first 30 Web sites, of which 22 diabetes and 21 depression sites met inclusion criteria (i.e., provided information for recruiting participants to a study). Because many Web sites listed more than one study, each study was examined separately. Specifically, of the 22 and 21 Web sites for diabetes and depression, respectively, 17 (77%) and 18 (86%) listed multiple studies, and five (23%) and three (14%) listed single studies.

Our search procedures yielded a total of 171 diabetes and 184 depression studies that we then analyzed. The goal of this sampling strategy was to obtain a sufficient number of Web sites in each category to be able to explore similarities, differences, and patterns that might appear. Each search was performed once in June 2006, with sites accessed on the same day (as results generated by search engines may change over time). All Web site and recruiting information was then printed and analyzed.

We examined and coded characteristics of the information on the Web sites, including mention of:

- whether the study was described as a clinical trial;
- whether a drug was administered or a device was used in the study, and if so, if these studies appeared to be more than minimal risk;
- any additional research procedures involving more than minimal risk (e.g., assessment procedures more invasive than drawing blood, such as lumbar puncture and electroconvulsive therapy (ECT), but not including the use of medications or devices, if these were already coded);
- whether sites mentioned the terms "risk(s)" or "side effect(s)";
- whether the sites referred in any other way to risk(s);
- any incentive (financial or nonfinancial);
- whether a financial incentive was offered, and, if one was, the specific amount that the participant

would be paid;

- whether a nonfinancial incentive was offered, and, if so, what it was (i.e., free treatment, medication, or evaluation);
- the number of visits involved in study participation;
- the length of the study; and
- the source of sponsorship (i.e., government, not-for-profit, or for-profit).

Since, as presented below, very few studies explicitly mentioned such source of sponsorship, we also assessed whether the contact person listed was at a for-profit or not-for-profit institution (revealed through affiliation on email or street address—e.g., a university vs. a pharmaceutical company). Finally, we assessed how financial incentives were presented in recruiting sites: whether mention of financial incentives used different font size or appearance (italics, bold, underline, or all capital letters) or other characters (exclamation points or asterisks) to emphasize this information.

We divided studies into two groups: those that appeared to involve more-than-minimal-risk intervention or assessment, and those that did not. We were guided by the assumption that studies in which medication is administered are generally more-than-minimal risk, due to the medication itself as well as possible assessment procedures. Studies that appeared to involve a more-than-minimal-risk intervention or assessment included those that administered medications or devices (e.g., insulin pumps, investigational devices, and transcranial magnetic stimulation—113 [66%] diabetes studies and 140 [76%] depression studies) or other active substances such as hormones or alcohol (two [1%] diabetes studies and two [1%] depression studies). They also included those that administered and/or mentioned an additional procedure other than administration of a medication or a device that involved more than minimal risk (specifically, muscle biopsy, gene transfer, intravenous catheter, intravenous infusion, and lumbar punctures—four [2%] diabetes studies and two [1%] depression studies). For diabetes, the four studies that listed additional, more-than-minimal-risk procedures also involved administration of a drug or device. Studies that did not appear to involve a more-than-minimal-risk procedure included those that administered vitamins, massage therapy, exposure to light, acupuncture, etc. We also included in this second group studies that involved ongoing use of psychoactive drugs (30% diabetes and 19% depression), since these studies did not appear to impose a higher degree of risk than the subject would otherwise encounter in his or her daily life. In all, the more-than-minimal-risk studies comprised 67% and 77% of the diabetes and depression studies, respectively. A research assistant coded the information on the sites, and decisions and any questions that arose were reviewed and resolved by the consensus of the team. We conducted Fisher's Exact Tests to determine differences between the two diseases on each of these characteristics and within each disease category to identify relationships among Web site characteristics.

Results

As shown in Table 1 (http://www.thehastingscenter.org/pdf/irb_2007_nov_dec_klitzman_tables.pdf), of the study descriptions for diabetes (N = 171) and depression (N = 184), most mentioned financial or nonfinancial incentives (73% diabetes and 75% depression). Fifty-four percent of the diabetes studies and 46% of the depression studies mentioned financial incentives only; 12% of the diabetes studies and 20% of the depression studies listed specific amounts. Forty-seven percent of the diabetes studies and 62% of the depression studies listed free medications or treatment as incentives. Only one study stated that no financial incentives would be offered.

Fewer than half of the studies examined reported study length (43% diabetes and 38% depression). Roughly one-third or fewer (34% diabetes and 18% depression) listed the number of visits required. Few studies mentioned a research procedure besides administration of a medication or device that appeared to be more-than-minimal risk (2% diabetes and 1% depression). None of the studies used the terms "risk" or "risks." The only use of the term "side effect(s)" was in reference to a study of "mild brain stimulation," in which the Web site stated, "Very weak currents are used to stimulate the brain. The stimulation is painless with no known serious side effects, and the person is fully awake and alert during 20 minute treatment sessions." Therefore, the term "side effect" was mentioned only to indicate that there were none in this study. Descriptions of nine studies (3%) altered the appearance of the text reporting financial incentives—three used bold, two used italics, one used capital letters, and one used an exclamation point. Of note, only 2% of the diabetes recruitment sites and 14% of the depression sites explicitly mentioned a source of funding.

Sixty-seven percent (N = 115) of the diabetes studies and 77% (N = 142) of the depression studies reported involving an intervention and/or procedure that appeared to be more than minimal risk (e.g., administering a drug or use of a device). As shown in Table 2 (http://www.thehastingscenter.org/pdf/irb_2007_nov_dec_klitzman_tables.pdf), of these, most (75% diabetes and 73% depression) reported an incentive. In addition, most were clinical trials conducted by a for-profit entity. Most also did not list number of visits or length of study, and only a few mentioned a procedure, other than administration of a medication or device, that appeared to be more-than-minimal risk.

Overall, as seen in Table 1 (http://

www.thehastingscenter.org/pdf/irb_2007_nov_dec_klitzman_tables.pdf), diabetes and depression studies did not differ significantly in the rates at which they listed any incentives, but other differences did emerge. Diabetes studies were less likely than depression studies to list nonmonetary incentives (i.e., free medications or treatment) or to involve any procedure (i.e., intervention or assessment) that appeared to present more-than-minimal-risk. They were also more likely to list the number of visits required and to be conducted by a for-profit entity. There was a trend for diabetes studies to list financial incentives more frequently than depression studies. Given these differences, we then explored within each disease category whether those studies that listed financial incentives differed from other studies (Table 1, http://www.thehastingscenter.org/pdf/irb_2007_nov_dec_klitzman_tables.pdf). For diabetes, those that listed financial incentives were more likely to list nonmonetary incentives as well, to give study length, and to involve any procedure that appeared to be more-than-minimal-risk. For depression, those that mentioned financial incentives were more likely to involve any procedure that apparently involved more-than-minimal risk and to list the required number of visits. For both diseases, presence of financial incentives did not differ between for-profit and not-for-profit studies, as indicated through either source of funding listed or institutional affiliation of contact.

For both diabetes and depression, those studies that appeared to involve a more-than-minimal-risk intervention were more likely to be clinical trials, to be funded or conducted by a for-profit entity, and to list a nonmonetary incentive.

Among studies that appeared to pose more-than-minimal risk, diabetes studies were more likely than depression studies to be clinical trials and to list number of visits. These diabetes studies also were less likely to be funded or conducted by a for-profit entity or to list a nonmonetary incentive and, as a trend, to list financial incentives and a specific amount.

We then examined the number of studies that mentioned an incentive of any kind but did not list either length of study or number of visits required for participation, and thus appeared to be providing an unbalanced view of the study. As indicated in Table 3 (http://www.thehastingscenter.org/pdf/irb_2007_nov_dec_klitzman_tables.pdf), we found that 38% of all studies (34% diabetes and 42% depression) fit this description. Diabetes and depression studies—both separately and when combined—that appeared to be providing such an unbalanced view of the study were more likely to be conducted by a for-profit entity ($p < 0.000$).

Discussion

Our examination is the first we know of to sample systematically online sites that recruit study participants and to do so by specific disease. We found that 38% (N = 136) of the sites (34% and 42% for diabetes and depression, respectively) did not appear to provide balanced descriptions of the studies. Nearly three-quarters of the sites appeared to provide more than merely "directory listing of descriptive information," in that they provided some description of incentives; yet roughly half of these failed to mention risks or what participation in the study involved (i.e., length of study or number of visits). No sites used the term "risk(s)," and only one site used the term "side effect(s)" (and then only to note their absence). Overall, most did not list length of study or number of visits. Even among studies that involved more-than-minimal-risk procedures, most did not mention what the study required, yet 75% of the diabetes studies and 73% of the depression studies mentioned an incentive, with 50% of the diabetes studies and 40% of the depression studies referring specifically to a financial incentive.

One might argue that the Web sites we examined provide only initial presentations of study descriptions and thus comply with the FDA and OHRP guidance, yet neither guidance includes incentives in its list of basic descriptive information that can be part of mere "directory listings."[20] The OHRP guidance also notes that any additional information should be "presented in a balanced and fair manner." Our data show that many online recruiting sites include some—but not full—descriptions of what will be involved for individuals who decide to enroll in the studies listed. Thus, the information provided appears inconsistent with federal guidance and weighted toward encouraging research participation.

One could also argue that persons who obtain information from clinical trial Web sites will receive additional data about potential research risks and requirements of participation during the informed consent process if they inquire further about participating in the studies listed. Yet although Web-based presentations about clinical trials are not formal informed consent documents, they represent initial contact with potential participants that may influence subsequent views and potential interest in enrolling. The federal guidance reflects this concern. Moreover, unlike advertisements in print media such as newspapers, Web sites have essentially unlimited space to present information regarding a study. In theory, Web sites used for recruitment could present a balanced picture of the tasks required and the potential risks involved, particularly when financial incentives are provided.

Of concern as well is the fact that recruitment Web sites that appeared out of balance were more likely to be sponsored by for-profit entities, and

that the majority of studies examined did not explicitly describe the research sponsor. Financial conflicts of interest are of increasing concern in biomedical research.[21] Prior studies have shown that most clinical trials are industry-funded, and that, of these, those that report that an author who published the study results had a conflict of interest were nearly five times more likely to report a positive result.[22] Hence, the source of funding for a study may well be important for potential study participants to be aware of, as it may affect the degree to which they trust investigators.

How might the problems we discovered be ameliorated? Federal guidance says that "IRBs should pay particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner." Insofar as many of the Web sites we studied went beyond basic descriptive information, they should have been subject to IRB review, but our data do not speak to the frequency with which review occurred. If IRBs were routinely involved, these results suggest that these IRBs have given insufficient attention to the content of study Web sites. In reviewing this material, IRBs should recognize that the inherent attributes of a Web site permit more information to be provided than is feasible in newspaper or radio advertisements. We are not suggesting that complete informed consent documents should be posted every time a clinical trial is advertised. Flooding potential subjects with information at an early stage of recruitment without having research staff available to respond to questions is likely to prove confusing. Rather, the goal, as reflected in federal guidance, should be balance in providing a realistic view of participation. To the extent that benefits or incentives are mentioned, the requirements associated with participation and potential risks should be noted as well. No template will fit every study, but the goal in each case is similar: to provide prospective subjects with a more complete picture of a study's sponsorship, benefits, risks, procedures, and enrollment incentives.

We note that modifying the federal guidance may help to accomplish this goal. By allowing "directory listings" to bypass IRB review, the current guidance encourages sponsors and investigators to limit the amount of information provided in Web-based contacts with potential subjects. The fact that information about incentives is nonetheless often included—though it does not meet the definition of "basic descriptive information"—suggests how difficult it may be to persuade researchers, in interactions with potential subjects, to refrain from "selling" participation in their studies. Were the OHRP and the FDA to recognize this reality, they might well modify their guidance to suggest that all outreach efforts, including directory listings, be reviewed prospectively by IRBs. The costs of such a process in delay and IRB workload should not be ignored, but in our view, the benefits to potential subjects of a more accurate understanding of what is entailed in joining a study are vital to consider.

This study has certain limitations. We examined only a portion of the Web sites that provide information about clinical trials, and we explored only two disease areas of clinical research. Although we have no reason to believe that these areas do not represent clinical research in general, further exploration of that question is warranted. Moreover, Internet practices are fluid. These results represent only a snapshot in time of recruitment Web sites. Ongoing monitoring and follow-up of this situation over time is clearly needed. Comparable studies of other venues in which clinical research studies are advertised would be helpful as well. Nonetheless, these data suggest that in their initial contact with studies, research participants recruited via the Internet may not receive balanced presentations of the implications of participation, and that at least the spirit, if not the letter, of federal guidance is often not followed. More IRB oversight should not be unduly burdensome and could help ensure that potential subjects receive sufficient and balanced information from clinical trial Web sites.

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