Recruiting Healthy Volunteers for Research Participation via Internet Advertising

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Objective: The Internet is frequently used as a tool to recruit research subjects, and the US Food and Drug Administration (FDA) provides general guidance regarding such advertising. The goal of this study was to explore the incidence and nature of ethically inappropriate recruiting advertisements on the Internet and to provide descriptive guidance to researchers for responsible Internet recruiting.

Methods: In this study, 119 advertisements recruiting health volunteers and listed on the CenterWatch Clinical Trials Listing Service website were reviewed for content as well as text style and visual effects.

Results: The majority of advertisements satisfied FDA guidance. However, 21 (18%) were ethically troubling with regard to font size, font style, and/or verbiage. In many advertisements, it was unclear if "medication" meant "investigational drug," "over-the-counter medication" or US FDA approved "prescription medication." Nearly 30% of the 119 advertisements used the terms "free," "no charge" or "no cost" as lures.

Conclusion: Ethically problematic recruiting advertisements can be coercive and misleading. Descriptive guidance provided in this paper can help clinical researchers create ethically appropriate recruiting advertisements.

Keywords: Advertising; Internet; Healthy volunteers; Recruiting; Research subjects

Once given visual form, any text is implicitly coded by that form in ways that signal, however subtly, its nature and purpose and how its creators wish it to be approached and valued.¹

Recruiting volunteers is an unavoidable, often time-consuming and difficult task in clinical research. Internet marketing of research studies occurs in various forms including websites dedicated to specific studies, clinical trial databases which store an aggregate of basic information about actively recruiting studies, and direct email solicitation to Listserves or target populations. Investigators and sponsors use Internet marketing because it potentially reduces their postage and printing costs, content delivery is instantaneous, and the amount of content is potentially limitless. While not all potential research subjects have personal computers with Internet access, such is available for free at virtually all public libraries. Even some hospitals have medical information libraries with computers dedicated specifically for patient use.²

Because clinical trial databases aim to recruit research subjects, they are a marketing tool, and therefore the content and visual appearance of the data entered are relevant to the concepts of coercion and deception. Specifically, words can be displayed in a variety of forms due to variations in the elements of the letter design (typography). Type style and use of bold font or slanting (italics) are forms of visual communication, and in this way, the typeface garners one's attention, speaks to the reader and even stimulates semantic meanings.³ As an example, car manufacturers carefully select their advertising fonts due to the meanings and associations they can project (e.g., elegance, power, confidence).^{3,4} Similarly, it has been argued that the "old fashioned" font style used by Wendy's (www.wendys.com), a US restaurant chain, may convey the feeling that their hamburgers are old fashioned and even wholesome.⁵

The US Food and Drug Administration (FDA) requires that institutional review boards (IRB) review and approve the materials and methods used to recruit human subjects,⁶ additionally, the FDA provides guidance regarding Internet

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Table 1. World Health Organization registration data set version 1.0.

Item	Entry Information
Study number	A unique number assigned to the study
Registration date	The date the study is entered into the database
Secondary number	Additional identifying number for the study
Funding source(s)	Identification of who is funding the study
Primary sponsor	Identification of the primary entity who is performing the research
Secondary sponsor(s)	Identification of the other sponsors of the study
Public query contact	Contact information for the general and recruiting information
Research query contact	Contact information for scientific information
Public title	Study title in lay language (for general public)
Scientific title	Scientific title of the study as approved by IRB
Countries of recruitment	Countries from which research subjects will be, plan to be, or have been recruited
Health issue(s) or problem(s) studied	Primary health condition or health prevention
Intervention	Description of the drug, device, and procedures involved in the study.
Key inclusion and exclusion criteria	Description of inclusion and exclusion, include age and sex
Study type	Randomized, cross-over, placebo-controlled, double-blind
Date of first enrollment	Anticipated or actual date of enrollment of first subject
Target sample size	Number of subjects planning to enroll in the study
Recruitment status	Pending, active, temporarily halted, or closed
Primary outcome	The main outcome used to determine the effects of the intervention(s)
Key secondary outcomes	Events, outcomes or experiences of secondary interest (e.g., hospitalization rate)

advertising.⁷ Specifically, the FDA does not require IRBs to review Internet listings of clinical trials as long as the listings provide only “basic trial information” (e.g., study title, study summary, study location, contact information). Internet databases that are designed with formal system limits (e.g., font size, font style, entry of only basic study information) satisfy this guidance, and thus, do not require IRB approval for each study listing. Two examples of such databases are the National Cancer Institute Physician Data Query Clinical Trials Database (<http://www.cancer.gov/search/clinicaltrials>) and the AIDS Clinical Trials Information Service (<http://www.aidsinfo.nih.gov/ClinicalTrials/Default.aspx?MenuItem=ClinicalTrials>). Both databases cross-link to another database (www.clinicaltrials.gov), with all three using a standardized data set consisting of 20 items that describe the study in detail (table 1).⁸

In the United States, nearly 46 million adults and children lack medical insurance,⁹ and it is from within this population pool that many individuals are selected to participate in research.¹⁰ It is impossible to quantify the number of healthy volunteers enrolled in studies as there is no national registry that tracks their participation (or their insurance status). Additionally, there is no consensus on the definition of “normal, healthy volunteer.”^{11,12} Their motivation to participate in research is often financial compensation or free medical exams,¹³⁻¹⁵ yet in the United States, for injuries

occurring during research participation, personal health insurance is the “primary vehicle for compensation,”^{16,17} putting the uninsured and underinsured who volunteer to participate in clinical research at risk of financial loss.

If the content of study advertisements is not automatically limited by software design (or manual approaches that ensure adherence to the “basic trial information” guidance), IRB review and approval should be obtained. This is because ethically inappropriate recruitment materials (e.g., those that use eye-catching visual cues or verbiage to promote study benefits) create the potential for prospective volunteers to underestimate or dismiss their risk of harm. This study explores the recruitment of healthy volunteers using a popular Internet database that does not use a standardized data set for study listings. The results of this study facilitated creation of Internet recruiting guidance that is applicable to all potential research subjects.

Methods

On March 8, 2006, the Centerwatch Clinical Trials Listing Service database (<http://www.centerwatch.org/patient/studies/phasei.html>) was reviewed for all studies recruiting “Healthy Patients” in the US. This service was selected for analysis because it is one of the oldest and most comprehensive Internet services of its type.¹⁸ As an open access (free) database, it catalogs over 41,000 research studies and does not use data entry system

limits as described above. Each study listing was reviewed to identify the font size and style (e.g., bold, italics, use of multiple fonts), visual effects (e.g., flashing text, logos, medical symbols) and general verbiage. In order to understand the study cohort being recruited and the potential risks to which they would be exposed, each listing was also viewed to identify the nature of the study (e.g., drug, device), population sought (adults, children) and study procedures, as well as the type of compensation offered for participating. Per Centerwatch policy, the content of each trial posting is written by each study's research team and approved by each facility's IRB. Centerwatch personnel do not conduct an ethics review of posting content and do not format the content to a standardized data entry set.⁸

Results

One hundred fifty-one recruitment advertisements were identified across 28 states. Of these 151 advertisements, one study site was closed for healthy volunteer enrollment, one was not enrolling healthy volunteers but rather adults with heart failure (database entry error), and one study site posted two identical recruitment advertisements for the same study site (database entry error). Subtracting these three, as well as identical advertisements that were repeated in the database because they were multi-centre studies, 119 unique advertisements remained for analysis.

Advertisement Design and Verbiage

No database advertisements contained special effects such as animation, flashing text or institutional/sponsor logos. Ten of 119 (8%) used words or sentences containing all capital letters in locations other than the study title. Three advertisements (3%) used exclamation points, three (3%) used bold font for words or phrases not in the study title or subheadings, and one (0.8%) used large font in an area other than the study title. The majority of advertisements satisfied FDA guidance. However, 21(18%) were ethically troubling with regard to font size, font style and/or verbiage (table 2). Fourteen of these 21 advertisements (not shown in table 2) were vague when describing the drug used in the research, using terms such as "medicine" or "medication" instead of descriptive terms such as "investigational drug," "over-the-counter medication" or "FDA-approved prescription medication."

Research Subjects

One hundred nine of 119 (92%) recruitment advertisements sought healthy adult participants, whereas 9 (8%) sought healthy pediatric participants (age 17 or younger). Seven advertisements (5%) did not specify if they were seeking adults or children. Because the target population of some advertisements (n=6) included adults, as well as children, the total exceeds 100%. Participants of any age were recruited for some studies (n=2), thus the potential high and low of the recruiting age range included the elderly, as well as infants.

Study Type and Procedures

Twelve of 119 (10%) advertisements were specifically

recruiting for vaccine studies. Of these studies, 4 were recruiting for HIV vaccine studies, 3 for genital herpes, 2 for human papillomavirus (both enrolling pediatric research participants), one for cytomegalovirus, one for meningitis and one for herpes simplex virus (pediatric participants). Fifteen of 119 (13%) advertisements were specifically recruiting for studies involving an "investigational drug." Four of 119 (3%) advertisements indicated the studies involved phase I research (drug, vaccine). The remaining advertisements either used vague terminology such as "infusion," "medication" or "medicine" to describe the agent under study (n=14). It is impossible to know how many of the 119 advertisements were recruiting for drug/device/vaccine and non-drug/device/vaccine studies because some ads were vague or completely nondescript in describing the nature of the study.

In addition to exposure to investigational drugs and vaccines, study procedures included but were not limited to blood withdrawal (26 advertisements), magnetic resonance imaging ("scan") excluding dual energy X-ray absorptiometry or other imaging excluding X-ray (14 advertisements), electrocardiogram (3 advertisements), glucose tolerance test (2 advertisements), bone marrow donation (2 advertisements), spinal tap (1 advertisement), saliva/mouthwash sampling (1 advertisement), breast duct lavage (1 advertisement at each of 12 study sites), bile sampling using a nasoduodenal tube (1 advertisement) and cytapheeresis (1 advertisement). Thirteen of 119 (11%) recruitment advertisements did not contain any description of the study activities.

Compensation

Specific compensation (e.g., dollar amount) for study participation was mentioned in 56 (47%) of 119 advertisements. Unspecified compensation (e.g., "You will be paid for your time") was mentioned in 33 advertisements (28%). The concept of compensation was not mentioned in 28 (24%) recruiting advertisements. Two advertisements (2%) indicated that no compensation was offered for participation. With regard to specific compensation, the largest amount offered was "up to \$4,280" for up to 8 weeks inpatient participation involving studying "medication effects." Other types of compensation offered included free group therapy, \$25 shopping mall gift certificates, \$10 bookstore gift certificates, smoking cessation classes, smoking cessation class referral, cholesterol testing, and meals, movies, reading materials and videogames during on-site research participation. One study site offered use of a 27 inch TV/DVD/VCR combination with satellite receiver during on-site participation.

Review of the compensation offered by the nine advertisements that were recruiting pediatric participants found that the highest specified compensation was \$40 (involved researchers observing the interactions of parents and their children). Three advertisements seeking to enroll pediatric participants indicated compensation would be provided but did not specify the amount. Two advertisements made no mention of compensation for pediatric participation.

Thirty-four of 119 (29%) advertisements used the words “free” [meals], “no charge” or “no cost” [exam] to describe research subject benefits. No recruitment advertisement for any study mentioned compensation for injuries occurring during study participation, and none mentioned if subjects were required to have their own health insurance as a condition of enrollment.

Discussion

In 2002, the Office of Inspector General (OIG) at the US Department of Health and Human Services generated a report summarizing their evaluation of various clinical trial web sites.¹⁹ While their study did not analyze the visual appearance of recruiting advertisements (e.g., font size, special text effects, use of exclamation points), they did analyze verbiage and determined that some advertisements contained “misleading information that can undermine informed consent.” Based on their findings, the OIG

recommended that IRBs review and approve advertising text that pertains to study risks and benefits.

The results from the current study indicate that the OIG recommendation does not go far enough, as the typology of recruiting advertisements can also be ethically problematic. Database recruiting advertisements can emphasize compensation and other benefits not only via the verbiage chosen, but also by text appearance (e.g., bold face type, block capitalization, italics), and this creates the potential for volunteers to focus on the benefits and underestimate or dismiss the risk of harm that can directly result from participation.^{20,21} In addition to the clinical impact, personal financial impact can be significant for the uninsured or underinsured as most studies do not provide free medical care to treat adverse events resulting from study participation.^{16,22}

Table 2. Problematic healthy volunteer recruiting advertisements.

CenterWatch trial #	Type of study	Study site	Study subjects	Advertisement issue
23159	Psychology (no drugs)	Academic medical center	Adults with history of being sexually abused	Use of bold font, italics, capitalizations, and exclamation point: “ FREE group therapy... earn up to \$250! ”
56830	Sexual health study (FDA- approved drug)	Academic medical center	Adult men	Problematic verbiage and exclamation point: “If you didn’t think healthy people could take part in clinical research trials, think again!”
70405	Pharmacokinetics (type of drug not indicated)	Contract research organization	“any age”	Problematic verbiage and use of capitalization: “If you have not contributed to medical research by age 30 you probably never will.” “TV/DVD/VCR combo with satellite in each room HELP TO ADVANCE MEDICAL RESEARCH.”
70547	Cytapheresis	United States Government research facility	Adults	Problematic verbiage: “Donors are asked to schedule repeat [cytapheresis] donations.”
83614	Psychology (no drugs)	Academic medical center	Adults and their children (age 7-13 years)	Use of bold font: “ You will receive \$40. ” “ ...transportation and parking fees will be paid for.... ”
84888	Investigational drug	Contract research organization	Adults	Problematic capitalization and verbiage: “CALL NOW”
85088	Psychology (no drugs)	Academic medical center	Adults	Problematic verbiage: “...you would be given a guaranteed \$20 and a chance to win more money (on average \$6).”

Data collected during this study also indicate that while recruitment advertisements seek “normal, healthy volunteers,” these same studies sometimes require the healthy volunteers to have a history of emotional and physical trauma,²³ be overweight,²⁴ be current tobacco smokers,²⁵ or current marijuana or heroin users.^{26,27} Are these people actually healthy? Might they be at greater risk with certain types of procedures or exposures to investigational drugs? Do addictions to tobacco, drugs or even food render people unhealthy from psychological, as well as physical perspectives? These are critical questions that research teams, sponsors, IRBs and the FDA must ponder when reflecting on study design and research subject safety.

Adverse events are a risk in all research studies, even those involving healthy subjects. A vivid example is that of the superagonist anti-CD28 monoclonal antibody (TGN1412) trial that triggered nearly fatal cytokine storm reactions in six healthy participants.²⁸ The data collected in the current research study indicate that healthy volunteers are being recruited for a variety of study procedures. Drug and vaccine studies pose the risk of allergic reaction, among other events (e.g., vomiting, fever, abnormal blood count, muscle wasting, seizure). In the case of human immunodeficiency virus (HIV) vaccine studies, HIV-negative subjects sometimes mistakenly believe that the vaccine provides protection against HIV infection, and then they engage in risky sexual behavior.²⁹ There is also a theoretical risk that the vaccine could enhance the ability of the virus to cause infection due to the creation of non-neutralizing antibodies.²⁹

Invasive techniques for specimen retrieval (e.g., spinal tap, bone marrow donation, cytapheresis) carry risks, as do experimental procedures such as special diets and exercise regimens. Imaging procedures using contrast agents have the potential for life-threatening reactions. Some risks, such as birth defects and fertility problems, might not evolve into

reality until after study participation is complete. Although rare, death can be a complication for healthy subjects participating in clinical research studies.³⁰⁻³² While investigators must be diligent about using the informed consent process to educate potential participants about study risks,^{33,34} a thorough informed consent process does not justify use of deceptive or coercive recruitment materials.

Not surprisingly, the data from this research study revealed no recruiting advertisements that mentioned the potential for adverse events or the plan for responding to (and paying for) research-related injuries. In the US, research institutions and sponsors are not required to compensate or provide free treatment to participants when they incur research-related harm. Few study sponsors and institutions automatically ensure free medical care to research subjects injured as a result of participating in their studies.³⁵⁻³⁹ Notably, the National Vaccine Injury Compensation Program excludes injuries resulting from the use of unlicensed [research] vaccines.⁴⁰

Conclusion

As mentioned, Centerwatch.org requires study site IRB approval for each study listing and does not, itself, conduct an ethics review of the content submitted by the research team. Thus, based on the data collected in this study, some IRBs approved ethically problematic recruitment material. For organizations such as Centerwatch.org that do not use database limiters, they should not rely solely on IRB approval from the study site, but they should also conduct an ethics review for each submitted posting. Admittedly this will incur time and cost burdens, but the benefit to potential research subjects and corporate integrity is ample justification. An alternative is for all database listings to contain a standardized data set, as detailed by the World Health Organization.⁸

Recruitment advertisements for healthy volunteers, as well as patients, should not overemphasize compensation or use

Table 3. Verbiage guidance.

Use “investigational drug” not “medication” or “medicine.” If the study involves a drug that is already FDA-approved, indicate this, as well as the new use/dosing under investigation.
Do not indicate that the purpose of the study is to provide any type of therapy, treatment, or cure.
Do not specify compensation (e.g., dollar amount) when recruiting pediatric subjects.
Do not use statements of heroism or bravado (e.g., “Support clinical research,” “Help us advance science”).
Do not use text effects (e.g., flashing text, animation, bold font, italics, capitalization) to promote concepts such as compensation or study benefits.
Do not use potentially coercive images or logos (e.g., mother holding a baby, older adult on a cruise, medical logos such as a caduceus).
Do not use the following phrases: “Hurry,” “Call now,” “We’re waiting to hear from you,” “Enrollment limited.”
Do not use exclamation points.
Do not use verbiage that inflates study benefits.
“Free,” “No charge,” and “No cost” should not infer that any of the benefits provided replace routine medical care that all humans need.

coercive or deceptive lures. All recruitment materials (e.g., Internet listings and websites, flyers for posting on bulletin boards) should be an honest snapshot of the research project and should not contain problematic text effects or verbiage (table 3). Advertising study remuneration is not unethical as long as it is not highlighted or emphasized causing it to stand out from other concepts in the advertisement. Also, the amount should not be coercive, but should reflect the burdens of study involvement.

Intentional vagueness of recruitment advertisements is also problematic. Terming an investigational drug simply as “medication” or “medicine” is misleading. Even the term “study medication” is vague and potentially misleading because there is no indication of its regulatory status. If a drug is not FDA-approved, it should be indicated as such or referred to as “investigational.” If an FDA-approved medication is being studied, its investigational use or dosing should be described. Recruitment advertisements should not attempt to offer medical care or cures, and they should not attempt to lure people into clinical studies as a replacement for routine medical care.

A limitation of the current study is that it did not include an analysis of sponsor-created recruiting websites (e.g., www.stepstudies.com). The content of such websites is vastly greater than that of a database listing, usually consisting of multiple web-pages that use text, audio and video to describe the study, its risks and benefits and testimonials from prior research subjects. Future research could analyze the content of a sampling of such websites. Additionally, future research could include focus group methodology to explore various advertising layouts (visual presentation including font size, style, verbiage) for the emotional responses triggered by the readers (including any ethical discomfort) and assessing the relationship of the emotional response to the likelihood of pursuing study enrollment.⁴¹ Ethical attention to the design of recruitment advertisements is critical to avoiding deception and coercion of potential research subjects.

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References

1. Gutjahr P, Benton M. Illuminating letters: Typography and literary interpretation. Amherst, MA: University of Massachusetts Press; 2001. 6.
2. Cain NJ, Fuller HJ. The hospital library online—a point of service for consumers and hospital staff: a case study. *Bull Med Libr Assoc* 1999;87:261-263.
3. Childers TL, Jass J. All dressed up with something to say: effects of typeface semantic associations on brand perceptions and consumer memory. *J Consumer Psych* 2002;12:93-106.
4. Brumberger ER. The rhetoric of typography: the awareness and impact of typeface appropriateness. *Technical Communication* 2003;52:224-231.
5. Unnava HR, Burnkrant RE, Erevlles S. Effects of presentation order and communication modality on recall and attitude. *J Consumer Res* 1994;21:481-490.
6. IRB review of research. Code of Federal Regulations. Title 21, Pt. 56.109(a), 2002 ed.
7. Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators 1998 Update. Recruiting Study Subjects. U.S. Food and Drug Administration Web site. Available at: <http://www.fda.gov/oc/ohrt/irbs/toc4.html>. Accessed May 11, 2006.
8. International Clinical Trials Registry Platform (ICTRP) Registration Data Set (Version 1.0). World Health Organization Web site. Available at: http://www.who.int/ictpr/data_set/en/index1.html. Accessed November 22, 2006.
9. DeNavas-Walt C, Proctor BD, Lee CH. Income, Poverty, and Health Insurance Coverage in the United States: 2004. U.S. Census Bureau, Current Population Reports, P60-229. Washington, DC: US Government Printing Office; 2005.
10. Vasgird DR, Hensleigh M, Berkman A, Schachne E, Trinh C. Protecting the uninsured human research subject. *J Public Health Manag Pract* 2000;6:37-47.
11. FAQs about Clinical Studies. National Institutes of Health Clinical Center Web site. Available at: <http://www.cc.nih.gov/participate/faqaboutcs.shtml>. Accessed March 23, 2006.
12. Guidelines for Medical Experiments in Non-Patient Volunteers. The Association of the British Pharmaceutical Industry Website. Available at: <http://www.abpi.org.uk/publications/pdfs/GLs-for-Medical-Experiments.pdf>. Accessed February 1, 2007.
13. Bigorra J, Banos JE. Weight of financial reward in the decision by medical students and experienced healthy volunteers to participate in clinical trials. *Eur J Clin Pharmacol* 1990;38:443-446.
14. van Gelderen CE, Savelkoul TJ, van Dokkum W, Meulenbelt J. Motives and perception of healthy volunteers who participate in experiments. *Eur J Clin Pharmacol* 1993;45:15-21.
15. Pickersgill A, Furniss H, Seif MW. Why do women volunteer to participate in clinical studies? *J Obstet Gynaecol* 1998;18:68-71.
16. The Lewin Group. Task Order Proposal No. 2: Care/Compensation for Injuries in Clinical Research. Contract Number HHS 100-03-0005. Falls Church, VA: The Lewin Group; 2005.
17. Ethical and Policy Issues in Research Involving Human Participants, Volume I. National Bioethics Advisory Committee Web site. Available at: <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf>. Accessed February 1, 2007.
18. Getz K, McDonald D, Heck D. Finding subjects on the internet. *Appl Clin Trials* 2000;9:S8-S11.
19. Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent. Report# OEI-01-97-00198. Department of Health and Human Services Web site. Available at: <http://oig.hhs.gov/oei/reports/oei-01-97-00198.pdf>. Accessed May 17, 2006.
20. Apseloff G, Ashton HM, Friedman H, Gerber N. The importance of measuring cotinine levels to identify smokers in clinical trials. *Clin Pharmacol Ther* 1994;56:460-462.
21. Apseloff G, Swayne JK, Gerber N. Medical histories may be unreliable in screening volunteers for clinical trials. *Clin Pharmacol Ther* 1996;60:353-356.
22. Steinbrook R. Compensation for injured research subjects. *N Engl J Med* 2006;354:1871-1873.
23. Trial Information. Summary: Surviving Childhood Sexual Abuse. CenterWatch Web site. Available at: <http://www.centerwatch.org/patient/studies/stu23159.html>. Accessed March 8, 2006.
24. Trial Information. Summary: Healthy Overweight Women Volunteers Needed. CenterWatch Web site. Available at: <http://www.centerwatch.org/patient/studies/stu62989.html>. Accessed March 8, 2006.

25. Trial Information. Summary: Healthy Tobacco Smokers Needed for Behavioral Studies. CenterWatch Web site. Available at: <http://www.centerwatch.org/patient/studies/stu71900.html>. Accessed March 8, 2006.
26. Trial Information. Summary: Healthy Marijuana Users Needed for Behavioral Studies. CenterWatch Web site. Available at: <http://www.centerwatch.org/patient/studies/stu85552.html>. Accessed March 8, 2006.
27. Trial Information. Summary: Healthy Users of Heroin (men and women, age 21-45 yrs) Needed for 4-8 Week Inpatient Study of Medication Effects. CenterWatch Web site. Available at: <http://www.centerwatch.org/patient/studies/stu72166.html>. Accessed March 8, 2006.
28. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;355:1018-1028.
29. Frey SE. Unique risks to volunteers in HIV vaccine trials. *J Investig Med* 2003;51:S18-S20.
30. Report of Internal Investigation into the Death of a Volunteer Research Subject. Johns Hopkins Medicine Web site. Available at: http://www.hopkinsmedicine.org/press/2001/JULY/report_of_internal_investigation.htm. Accessed March 10, 2006.
31. Historical information on Duloxetine hydrochloride (market as Cymbalta). FDA Alert: Suicidality in Pediatric and Adult Patients [Issued 6/2005]. U.S. Food and Drug Administration Web site. Available at: <http://www.fda.gov/cder/drug/infopage/duloxetine/historical.htm>. Accessed February 2, 2007.
32. Wentzel M. The death of a healthy college student volunteer in a research study: Case history, analysis, lessons. *Clinical Trials Advisor Newsletter, Supplement*. Naples, FL: Global Success Corporation; 1996.
33. Tishler CL, Bartholomae S. Repeat participation among normal healthy research volunteers: professional guinea pigs in clinical trials? *Perspect Biol Med* 2003;46:508-520.
34. Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators 1998 Update. 21 CFR Part 50 – Protection of Human Subjects. Elements of informed consent. U.S. Food and Drug Administration Web site. Available at: <http://www.fda.gov/oc/ohrt/irbs/appendixb.html>. Accessed February 2, 2007.
35. What We're Doing: Policy on Compensation to Human Research Subjects. Pfizer Web site. Available at: www.pfizer.com/pfizer/subsites/corporate_citizenship/ethical_trials_human.jsp. Accessed March 13, 2006.
36. Title 38: Pensions, Bonuses, and Veterans' Relief. Part 17.85: Treatment of Research-Related Injuries to Human Subjects. Available at: <http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=b0d28c686f0ba71d40da7ceb715f7fb5&rgn=div8&view=text&node=38:1.0.1.1.19.0.178.47&idno=38>. Accessed February 2, 2007.
37. University of Washington Human Subjects Manual. VII. Special Topics: Section VII-G: Compensation for Adverse Events. University of Washington Web site. Available at: <http://www.washington.edu/research/hsd/hsdman7.html#VII-g>. Accessed March 2, 2006.
38. Research Related Injury – Operational Policy and Procedure. Wake Forest University School of Medicine Institutional Review Board. Wake Forest University Baptist Medical Center Web site. Available at: <http://www1.wfubmc.edu/NR/rdonlyres/16D980D3-AD27-41B8-95AB-827FE4E2F86B/0/CoverageforResearchRelatedInjuryPP.pdf>. Accessed March 2, 2006.
39. Investigator's Manual for the Protection of Human Subjects. Section 4-12: Emergency Care and Compensation for Injury. University of California Los Angeles Office for Protection of Research Subjects Web site. Available at: <http://www.oprs.ucla.edu/human/manual/hspcmanual/4C#Ch4Ck>. Accessed March 2, 2006.
40. National Vaccine Injury Compensation Program (VICP). U.S. Department of Health and Human Services Web site. Available at: www.hrsa.gov/vaccinecompensation. Accessed March 2, 2006.
41. Hilton Jr TA. How to test your headlines without spending a fortune in advertising fees. International Cyber Business Services, Inc. Web site. Available at: http://www.icbs.com/Kb/marketing/kb_how-to-test-your-headlines.htm. Accessed December 5, 2006.

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