Permitted research involving prisoners (§46.306)

- If prisoners will be assigned to control groups which may not benefit, approval of HHS Secretary must be obtained via published notice in Federal Register.

Practices with intent & reasonable probability of improving health or well-being of the subject

- Possible causes, effects, and processes of incarceration, and of criminal behavior

- Conditions particularly affecting prisoners
  i.e. diseases, social and psychological problems more prevalent in prisons

- Study of prisons as institutional structures or of prisoners as incarcerated persons

§46.304 Composition of Institutional Review Boards where prisoners are involved (In addition to 45 CFR 46.107)

- At least one prisoner, or a prisoner representative
- Majority of the Board (exclusive of prisoner members) has no association with the prison(s) involved
Approval Criteria for Research involving Prisoners (§46.305)

- Risks would be acceptable to non-prisoners
- Information is presented in language understandable to population
- Participation has no effect on parole
  *Prisoners must be clearly informed of this in advance*
- Advantages to participation will not impair ability to weigh risks
- Adequate provision for follow-up; taking length of sentences into account
- Selection of subjects is fair to all prisoners
  *Unless PI justifies otherwise in writing, control/treatment group assignment must be random*
Brenda L. Curtis  
*Treatment Research Institute, Philadelphia*

**ABSTRACT:** *social networking sites and online advertising organizations provide HIV/AIDS researchers access to target populations, often reaching difficult-to-reach populations. However, this benefit to researchers raises many issues for the protections of prospective research participants. Traditional recruitment procedures have involved straightforward transactions between the researchers and prospective participants; online recruitment is a more complex and indirect form of communication involving many parties engaged in the collecting, aggregating, and storing of research participant data. Thus, increased access to online data has challenged the adequacy of current and established procedures for participants’ protections, such as informed consent and privacy/confidentiality. Internet-based HIV/AIDS research recruitment and its ethical challenges are described, and research participant safeguards and best practices are outlined.

**KEY WORDS:** ethics, Internet research, online recruitment, social media, privacy, informed consent

*Received: August 21, 2013; revised September 11, 2013*

**SOCIAL NETWORKING SITES SUCH AS MYSPACE,** Facebook, Twitter, Grindr, Google+, and LinkedIn have changed how people interact with one another. Users are able to provide real-time information about their daily lives from their computers, tablets, and cell phones. In 2012, 81% of adult Americans used the Internet, 85% owned a cell phone, and 67% used social networking sites (Duggan & Brenner, 2013).

Social networking sites have created a new “HIV risk environment” where people can seek to evaluate risk of infection and negotiate safer sex practices prior to meeting potential partners (Fishbein et al., 2004; Hennessy et al., 2007; Hooper et al., 2008; Horvath, Rosser, & Remafedi, 2008; Rietmeijer & McFarlane, 2008). Social networking sites also provide an “HIV research environment” where participant recruitment, behavioral surveillance, and interventions have taken place (Beymer, 2012; A. M. Bowen et al., 2008; Bull et al., 2011; Burrell et al., 2012; Fernandez et al., 2004; Jaganath et al., 2012; Ko et al., 2013; Landovitz et al., 2012; Rice et al., 2012; Voytek et al., 2012; Young & Jaganath, 2013; Zhang et al., 2008). While research utilizing social networking sites provides HIV researchers access to people representing almost every group within society (Nosek, Banaji, & Greenwald, 2002; Subrahmanyan et al., 2008; Thelwall, 2008), use of this technology has challenged the adequacy of participant protections provided through traditional informed consent, privacy, and confidentiality procedures. It has also called into question the validity and reliability of the data collected.

Internet recruitment efforts, particularly those that use social networking sites, are increasing in prevalence because they allow the researcher the ability to better target their intended audience (Fernandez et al., 2004). Researchers rely on the many tools provided by social networking companies to target participants and collect data, and the information provided by potential participants can in turn be used by the social networking companies for other purposes. While this targeting may result in greater efficiencies, it also raises ethical concerns because information that may traditionally be thought of as private and personally identifiable is gathered before the participant is enrolled in the study. In addition, many individuals are unaware that the act of showing interest in a research study through clicking on a recruitment advertisement is providing data to third-party companies and leaving an identifiable trail. Researchers and ethics committees are also often unaware of the privacy risks involved. This should be of particular concern to HIV and AIDS researchers due to the sensitivity of the topic, where privacy and confidentiality are key elements of the relationship of trust and respect that exist between the researcher and the participant.

As an example, DoubleClick was used in a recent CDC national campaign, “testing makes us STRONGER,” promoting HIV testing among black gay and bisexual men. DoubleClick, an advertising company that is owned by Google, deposits small persistent
“cookies” (which contain unique alphanumeric codes) on users’ computers. These persistent cookies remain on the users’ computers after they have left the site and turned their computers off. Persistent cookies are used with session cookies to trace users as they move about the Internet in order to deliver targeted ads with the assistance of web beacons. Web beacons are embedded into websites and are not seen by the viewer. These tracking tools enable the website owners to know what content the user has viewed. This information is pooled across the many websites a user has visited and combined with information the user supplies to websites, forming a data profile that is made available to third-party advertisers.

When a user clicked on the “testing makes us STRONGER” ad, DoubleClick was immediately provided with (at a minimum) information that the user was interested in HIV testing. A click on the ad also increases the probability that the user will be identified by DoubleClick as black and gay or bisexual. DoubleClick maintains that the personal information it collects includes (but is not limited to) “name, address, telephone number, email address, social security number, bank account number, and credit card number” (www.google.com/doubleclick/). DoubleClick’s privacy policy states they will obtain a user’s consent to (1) link their name or personally identifiable information to their DoubleClick cookie and (2) associate their DoubleClick cookie with sensitive topics such as race, religion, sexual orientation, and health. It is clear from the example above that, in some instances, by clicking on the “testing makes us STRONGER” ad, individuals may have unknowingly added personal and sensitive information to their persistent cookie that subsequently became part of their online profile that is available to third-party advertisers, businesses, and researchers who use an online company to send ads to black and gay or bisexual men and persons who might be interested in HIV testing.

The Uniqueness of Online Recruitment

The technique used by DoubleClick is called online behavioral advertising (OBA). OBA reflects a broad range of activities that companies use to collect information about our online activities (e.g., webpages we visit, links we click on, and search terms we use). The tracking, collection, and sale of online information occur every day and much of this information is provided by the individual user. However, the user may not know this information is being collected and sold and that, currently, few legal regulations exist. With the privatization of research and advances in online marketing, recruitment has increasingly become a business, and many niche-market companies have established themselves as recruitment experts (Epstein, 2008; Wright, 2006).

Researchers have turned to this online advertising industry to reach potential participants (Bull et al., 2011; Carpenter et al., 2011; Curtis, 2012; Graham et al., 2008; Hagan, 2010; Voytek et al., 2012). OBA companies give researchers the tools they need to effectively recruit many hard-to-reach populations into research studies. Typical information available to researchers upon which they can build a sample include, but is not limited to, demographic data, education, employment history, interests, location histories, and topics the user has searched on in the past (see Table 1).

While there are similarities between traditional recruitment (hard-copy flyers, mailed materials, in-person meetings) and Internet recruitment, Internet recruitment is a fundamentally different recruiting technique, and this technique is further complicated by social networking sites and the use of OBA. For example, social networking sites are able to use OBA to aggregate individual online activities and personal data obtained from individuals, their families, and friends to create individual user profiles that contain sensitive and personal information (see Table 1).

<table>
<thead>
<tr>
<th>TABLE 1. Information Collected by Profiling Services and Ad Networks and Made Available to Researchers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>Employment history</td>
</tr>
<tr>
<td>Broad and specific interest</td>
</tr>
<tr>
<td>Location-based search history</td>
</tr>
<tr>
<td>Past search history</td>
</tr>
</tbody>
</table>
A DIFFERENT TRANSACTION

In the past, recruitment tended to be a relatively untargeted public call for research participants displayed in traditional media such as newspapers or radio announcements, university bulletin boards, or on the sides of subways and buses (Figure 1). Traditional recruitment model was a straightforward transaction between the researcher and the prospective participant: an researcher posted or purchased an advertisement and a prospective participant, who saw the advertisement and was interested, contacted the researcher—normally by phone.

In addition to the simplicity of this transaction, there was widespread familiarity with the logistics of each step in the process. Researchers generally knew what was involved with placing an advertisement and were familiar with the technology and the parties involved in the transaction. Because of this familiarity, both researchers and ethics committees could realistically be expected to understand the ethical considerations of a recruitment program and act accordingly.

Online recruitment is a much more complex transaction. Not only are there many more parties involved in any single transaction online, but the transactions tend to be much more opaque. Jon Leibowitz, chairman of the Federal Trade Commission in 2009, produced a set of "data flow charts" to demonstrate to the consumer the practices employed by social networking, cloud computing, online behavioral advertising, mobile marketing, and the collection and use of information by retailers, data brokers, third-party applications, and other diverse businesses. What should be of particular interest to HIV researchers and ethics committees is the circular transmission of information (Figures 2 and 3). The online behavioral advertising ecosystem (e.g., Google search engine ads, website banner ads) details the transmission and aggregation of profile, demographic, interest, and behavior data through the use of tracking software to create highly individualized and detailed user profiles that are made available to ad networks, merchants, and secondary ad networks (Figure 2). For the social networking chart (Figure 3), when a person clicks on an ad (e.g., interest in participating in an HIV study for MSM), this information is sent back to the ad servers and third-party apps and a person's public facing profile may also contain this information (e.g., "Like" feature on Facebook).

It can be extremely difficult to discern the interests, ethical guidelines, or even the participating parties in any given online transaction (flow of information). Additionally, every online transaction is routinely captured as data, disseminated, and increasingly aggregated into ad networks, analytic providers, merchants, and profiling services databases. What used to be a relatively simple and confidential process is now rife with the potential for unintended disclosures. As the technology continues to evolve, not only will more parties join this transaction, but the quality and quantity of the data

FIG. 1. Example of a Traditional Recruitment Advertising Transaction.
Online Recruiting for HIV Research

FIG. 2. Online Behavioral Advertising.
Fig. 3. Social Networking Advertising.
collected by and available to these parties will increase. While this increased access to data allows researchers to target online recruiting to segments of the population that are oftentimes hard to reach by traditional recruiting techniques, it presents a challenge to researchers and ethics committees seeking to quantify and qualify the ethical considerations of online recruitment.

**REACH**

Another difference between online recruitment and traditional print recruitment advertisements is “reach,” which refers to the number of different people who are exposed to an advertising message at least once. “Coverage” is the potential number of people exposed to an advertising message. Reach is limited by the circulation’s coverage area (posting of flyers, direct mail, newspapers, and magazines). On the Internet, a single website or online advertisement can, in principle, reach participants anywhere in the world—that is, have global coverage. Online advertisements can potentially recruit participants from more places and allow researchers to recruit participants far outside their local area.

The population of participants HIV researchers are interested in reaching are oftentimes participating in risk-taking behaviors that are stigmatized or illegal in the society at large. This results in the lack of a cohesive geographic sampling frame from which to recruit a sample or “subpopulation.” These “hidden subpopulations” are crucial to preventing the spread of HIV (Magnani et al., 2005). Social networks on the Internet allow for recruitment of these “hidden subpopulations” by using snowball sampling strategies (ibid.) through advertising on interest-targeted (e.g., MSM) blogs, message boards, and drug use, dating, and social networking sites such as Grindr, Facebook, Adam4Adam, BlueLight, and Drugs-Forum.com (A. Bowen, Williams, & Horvath, 2004). This increased reach and coverage has given HIV researchers access to these hard-to-reach subgroups of people.

**Examination of Online Recruiting for HIV Research and Best Practices**

Investigators and ethics committees are facing major challenges in the research environment due to use of the Internet as a participant recruitment tool (Buchanan & Ess, 2009; Buchanan & Hvizdak, 2009). Online behavioral advertising techniques and increased reach raise ethical, implementation, and logistical issues for investigators and ethics committees. According to Fowler-Dixon, “this new emphasis on Internet research has left some IRBs looking for ways to catch up to the technology and to learn how to approach the special challenges involved” (“Internet research raises unique ethical concerns for IRBs,” 2008, p. 25). These challenges that relate to online recruiting have been categorized into two types of ethical issues: privacy and confidentiality and informed consent (Buchanan & Ess, 2009; “Internet research raises unique ethical concerns for IRBs,” 2008). The following sections examine these ethical challenges for online recruitment within four popular contexts: search engines, websites, social network sites, and e-mail.

**PRIVACY AND CONFIDENTIALITY**

Respecting participants’ rights to privacy is a fundamental principle guiding national regulations across the world (Rehman, 2010). For example, in the United States, “The Right to Privacy” was one of the most influential law journal articles of the nineteenth century, in which Samuel D. Warren and Louis D. Brandeis (1890) described their frustration with how newspapers, then considered a new technology, had increased journalists’ abilities to report on the private lives of individuals. In their article, privacy was defined as “the right to be let alone” and characterized as a freedom from exposure to or intrusion by others, and they argued that current laws and regulations inadequately addressed threats to privacy caused by the use of the new technology. In a series of decisions, the U.S. Supreme Court affirmed that there is, indeed, a right to privacy in the United States that is contained in the “penumbras” and “emanations” of other constitutional protections (Griswold v. Connecticut, 1965). This right has been extended to the right of information privacy which allows individuals to limit the kinds of information that others know about them (Stevens, 2001).

When HIV researchers are collecting data online, it is important that they have control over access to this information and that they do not compromise the confidentiality of the data and the privacy of the participant before consent into the research study. There are three main confidentiality and privacy threats arising from using social networking sites for recruiting subjects into HIV studies (see Table 2): (1) lack of confidentiality when evaluation data are collected online; (2) poor user privacy and confidentiality protections of social networking sites; and (3) threats related to the collection of protected health information.

Using a study where at-risk Hispanic men who have sex with men were recruited to participate in
community-based HIV studies as an example, recruitment occurred in online chat rooms (Fernandez et al., 2004). Recruiters used a script that consisted of five parts: (1) introductions; (2) preliminary screening process (ethnicity, gender, sexual preference, location, age); (3) consent to proceed; (4) study description; and (5) procedures for enrollment (sending participant to another page to complete a contact form). Because these communications occurred in the online chat rooms, the transcripts of the chat sessions were available to the social networking site provider and to any third party that the site allowed access.

In another HIV prevention study, among predominantly minority youth, researchers required participants to “like” the study’s Facebook page after they were assigned to a study condition and to recommend the study to three Facebook “friends” (Bull et al., 2011). Although the researchers report they did not allow participants to be their friends, because they did not want to have access to the personal information on the participants’ profile pages, they actually may have had access to this information inside Facebook Insights—depending on when Facebook introduced this feature to Insights and when the researchers conducted the study. Facebook stores “like” information and makes this information available to the page administrator and to advertisers. Page administrators, if they chose to, can view their “likes” photos and profiles (Figure 4).

Table 2 presents recommendations for addressing the three main confidentiality and privacy threats. These best practices include: (1) allowing the study team sole access to identifiable data; (2) using ID numbers instead of user profile names when online data are collected; (3) not connecting participants to the study’s social networking site; (4) not using contact forms and signup forms inside social networking sites; (5) regularly reviewing participant posts to ensure identifiable information is not posted; and (6) ensuring any protected health information is collected according to national and international requirements. Researchers must regularly review terms of agreement, privacy and confidentiality policies, and features available to advertisers, businesses, and other third parties for companies they plan to use during the recruitment process. Researchers should contact these companies and ask them to remove from their databases any information pertaining to the study—including which users received, viewed, and responded to the recruitment advertisements. In addition, researchers should use landing pages that are secured to prevent the capturing of any user information—including responses and page viewing history.

### Table 2. Confidentiality and Privacy Recommendations.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Best Practice</th>
</tr>
</thead>
</table>
| There is little control over confidentiality in situations where evaluation data are collected online. | 1. Identifiable data from online assessments should be accessible only to the study team.  
2. ID numbers can be assigned to participants offline and all online information about participants is accessed via this number. |
| Social networking sites with poor privacy and confidentiality protections (e.g., Facebook and Instagram members’ confidentiality rights). | 1. Research teams should not invite participants to be their online “friends” or to “like” them—thus they will not have access to personal information on profile pages and can only access information that participants make publicly available.  
2. The “Contact Us” and/or “Sign Up” should not be located on social networking sites. When researchers would like participants to sign up or to invite their friends to participate, the research team should send prospective participants to a site landing page that is secure and not connected with the social networking site.  
3. If participants are allowed to post information to the study social networking site, postings must be monitored multiple times each day and identifiable or inappropriate information should be removed.  
4. Regularly review sites’ privacy and confidentiality policies and advertiser, business, and third-party features. |
| The collection of health information (Health Insurance Portability and Accountability Act [HIPAA] regulated). | 1. All assessments should be collected through a secured Internet site, not housed by social networking sites.  
2. Storage and transfer of electronic data must use current standards of encryption, password protection, and be stored behind a secure firewall. |
INFORMED CONSENT
At minimum, the informed consent must include the following information necessary for a potential participant to make an informed, rational, and voluntary decision: (a) the risks and potential benefits of research participation; (b) the extent and limits of confidentiality protections; and (c) the right to refuse to participate and to withdraw from the research without penalty or loss of benefits to which the participant is otherwise entitled (Krogstad et al., 2010; Stultiens et al., 2007).

Using the Internet to recruit research participants for HIV prevention and intervention research presents several concerns regarding consent (see Table 3). Many countries have national regulations that do not permit children or adults who have been declared legally incompetent to consent to research participation without the permission of a guardian (Krogstad et al., 2010; Stultiens et al., 2007). However, when a person is recruited online and consent is obtained electronically, it is difficult, if not impossible, for a researcher to verify the age, competency, and comprehension of the potential participant. This is of special concern regarding topics covered in HIV research (e.g., HIV risk topics including drug use, commercial sex work, human trafficking, and other sexual activity), and the possibility of minors responding and participating to an online study involving inappropriate materials for their age without the researcher’s knowledge. These challenges are not unique to the Internet. For example, the stock screener question “Are you at least 18 years of age?” used in both telephone and mail surveys is not a reliable way to verify the validity of a prospective participant’s status as an “adult” who can give legal “consent.” Yet, there are several techniques available to researchers that allow for age verification through cross-checking with other available information (see Table 3). Most social networks have software tools that allow almost any website or third party to authenticate users and verify age through their system (e.g., Facebook Connect, Twitter API, and Google Accounts).

Improving How We Evaluate Consent Comprehension. Traditional forms of recruitment have the same problems regarding competency and comprehension. To assume otherwise, assumes that visual cues are adequate to judge whether a person can understand the consent information. In this regard, online recruitment creates a unique opportunity to allow for computerized ways to ensure the informed consent process is understood. HIV researchers oftentimes work with drug using populations, populations with limited English proficiency, and those with psychiatric problems. Through methods similar to a “teaching then testing” technique used in substance abuse research (Aldridge & Charles, 2008), HIV researchers can produce web-based interactive and consent procedures. Educational design principles can be used to support learning and comprehension of the study information, procedures, risks, and benefits.
Participants can view this information at an educational level and language specifically tailored to them; and they can be asked to demonstrate competency before they are able to advance. When participants report incorrect information, they can receive corrective feedback; the specific information they are having problems understanding can be viewed again (or they may choose to withdraw from the process). This tailoring of the consent content to meet the educational and language needs of participants through the use of audio-visuals and to assess comprehension are features unique to the use of an online consent process. The use of technology also allows for participants to provide researchers with information about the consenting procedure so that their experiences can be fed back into the system and to allow for the adaption of information—promoting content that is easy to understand (Table 3).

**Conclusion**

Internet-based recruitment allows researchers to reach concealed, disparate, vulnerable, and hidden populations (Kirchhoff & Kehl, 2007; Souder, 2009). This ability to include hard-to-reach populations is one of the fundamental principles of research ethics, “justice,” as defined in the Belmont Report (1979); research ethics also requires researchers to maximize possible benefits from the research and minimize burdens to their participants. “Benefits” are gains to society or science through a contribution of factors that include empowerment of the individual by giving him or her voice and useful information as well as treatment. These ethical requirements have especially important consequences for “vulnerable” groups of research subjects.

According to established standards of practice, research should be designed with administrative, management, and technical safeguards to control authorized use and disclosure of information and to protect against unauthorized disclosure of information. As a general principle, information is not to be disclosed without participant consent. However, due to the increasing use of online behavioral research advertising, specifically social networking sites, concerns are warranted regarding the researchers’ responsibilities to actively protect against disclosure of private information, not just for their own purposes but for third-party service providers. As online recruitment employs a range of behavioral marketing techniques—search engines, websites, social networks, various forms of instant messaging, and e-mail—researchers, research participants, and ethics committees will encounter ethical questions only broadly covered in current regulations. These challenges are likely to relate to privacy and confidentiality, informed consent, and the collection of valid and reliable data. For example, the mere clicking on an advertisement to find out more about an HIV vaccine research study may disclose a person’s sensitive and private information (be it accurate or not) that is likely to be recorded and combined with a person’s online user profile—all of this before the formal

<table>
<thead>
<tr>
<th>TABLE 3. Informed Consent Recommendations.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Informed Consent</strong></td>
</tr>
<tr>
<td><strong>Issue</strong></td>
</tr>
<tr>
<td>Comprehension of study information,</td>
</tr>
<tr>
<td>procedures, and informed consent form.</td>
</tr>
<tr>
<td>1. Participants can be provided a brief</td>
</tr>
<tr>
<td>summary of the consent, linked to the</td>
</tr>
<tr>
<td>detailed consent, and e-mailed a copy of</td>
</tr>
<tr>
<td>the consent.</td>
</tr>
<tr>
<td>2. Facts about the study can be</td>
</tr>
<tr>
<td>shortened into digestible FAQs that are</td>
</tr>
<tr>
<td>on the study landing page. An FAQ section</td>
</tr>
<tr>
<td>can also be placed on the social</td>
</tr>
<tr>
<td>networking site page.</td>
</tr>
<tr>
<td>3. Participants can be asked to provide</td>
</tr>
<tr>
<td>feedback about the information provided</td>
</tr>
<tr>
<td>so that researchers can adapt the</td>
</tr>
<tr>
<td>information to be better understood.</td>
</tr>
<tr>
<td><strong>Best Practice</strong></td>
</tr>
<tr>
<td>Legal age</td>
</tr>
<tr>
<td>1. Age verification through cross-checking</td>
</tr>
<tr>
<td>with other information (e.g., Facebook</td>
</tr>
<tr>
<td>Connect; parents, guardians, schools, or</td>
</tr>
<tr>
<td>third parties vouching for minors).</td>
</tr>
<tr>
<td>Competency</td>
</tr>
<tr>
<td>1. Online quiz regarding the content of</td>
</tr>
<tr>
<td>the consent form and purpose of the study</td>
</tr>
<tr>
<td>to validate competency (and comprehension)</td>
</tr>
<tr>
<td>2. Correct answers to quiz questions</td>
</tr>
<tr>
<td>required before participant can proceed</td>
</tr>
<tr>
<td>to study.</td>
</tr>
</tbody>
</table>
informed consent process has been initiated by the researcher. Therefore, researchers’ research practices should aim at reducing the possibility of disclosures of private information, and ensuring that informed consent is obtained and that data are reliable and valid. Ethics committees should be aware of these issues so that they are able to regulate the flow of private information, thus minimizing potential risks to the research participants in studies they review.

**Best Practices**

Below are 10 recommended or “best” practices for social networking and online recruiting of participants for HIV research.

1. All data assessments should be collected through a secured Internet site that is outside of the social networking site, and data should be accessible only to the study team. This includes “contact us” forms and pre-screening questions.
2. Researchers should not ask participants to e-mail contact information or survey data as that is not a secure form of communication (Buchanan & Hvizdak, 2009).
3. Researchers will stay abreast of social networking sites and advertiser privacy and confidential policies and terms of service. Researchers are cautioned in conducting recruitment with adolescents and/or on sensitive/illegal topics on social networking sites with a history of poor privacy and confidentiality policies.
4. By spending time learning about the features available to businesses and third-party advertisers, researchers will have a better idea of what data are being collected and sold about users of that social networking site.
5. Researchers will contact social networking sites and ask them not to record (or immediately delete) data regarding their advertisements.
6. Health information will be collected and stored according to the national and international regulations.
7. If participants are allowed to post information to the study social networking site, postings will be monitored multiple times each day; identifiable or inappropriate information will be removed.
8. Researchers will avoid asking participants to “like” their study page and sending their online “friends” invites to join the study through the software provided by the social networking sites.
9. There are techniques to verify age and authenticate users on most social network sites. Researchers can also use offline techniques to verify age and authenticate users.
10. Informed consent comprehension and competency can be improved through the use of interactive consenting procedures that provide corrective feedback and are tailored to the users’ educational and language preferences. Participants can be provided with various versions of the consent form—one version can be brief with hyperlinks to the more detailed version.

**Educational Implications**

Educational offerings such as workshops and webinars for ethics committee members and HIV researchers could be designed to enhance their abilities of developing and accessing online recruitment strategies. Using this adapted set of questions that Ess (2005) and Buchanan (2010) recommend we ask when undertaking Internet research, ethics committees and HIV researchers will be able to address participants’ privacy and confidentiality concerns and issues of transparency in connection with online behavioral advertising and social networking sites.

Where does the interaction/communication/study take place? What ethical expectations are established by that venue?

- The greater perceived privacy of the participant and/or the less privacy afforded by the venue, the greater need to protect individual privacy, confidentiality, right to informed consent, etc.

Who are the participants?

- The greater the vulnerability of the participant, the greater the obligation of the researcher to protect the participant.

When will the informed consent process start?

- Ideally, protecting participants’ rights to privacy, confidentiality, autonomy, and informed consent should start at the beginning of any data collection.

How long does the third-party provider and ISP preserve the data and where?

- The researcher should make every effort to (a) not store data by ISPs and third-party providers and
(b) if it is being stored, have the data removed as soon as possible.

What third-party policies impact the research?

- Has the researcher read the terms and services of the sites and providers? Can the researcher provide adequate information to the participants and/or ethics committee concerning how the third party will protect their data?

Is the researcher able to provide control to the participant?

- All behavioral advertising practices should contain clear descriptions of online advertising practices and provide the participant with the ability to opt-out (or opt-in in the case of ISPs and toolbar applications) of such practices. Researchers should test to ensure they work and the participant can truly opt-out/in.

Research Agenda

Challenges to the ethical conduct of online recruitment will continue to evolve rapidly as the online technology evolves and as societal privacy concerns and research regulatory structures change throughout the world. Research should continue to track and evaluate informational risks, and to seek procedural solutions to the protection of the confidentiality of data and the personal privacy of those whose data are captured for research purposes.

Acknowledgments

This paper was supported in part by the Fordham HIV Prevention Research Ethics Training Institute (RETI), a five-year training grant sponsored by the National Institute on Drug Abuse (#1R25DA031608-01, Principal Investigator, Celia B. Fisher, Director Center for Ethics Education). The content is solely the responsibility of the author and does not necessarily represent the official views of the Treatment Research Institute or the Fordham HIV Prevention Research Ethics Training Institute.

Author Note

Address correspondence to: Brenda L. Curtis, PhD, MSPH, Health Communication Research Scientist, Treatment Research Institute, 600 Public Ledger Blvd., 150 Independence Mall, Philadelphia, PA 19106. Phone: 215-399-0980; Fax: 215-399-0987; e-mail: bcurtis@tresearch.org

Author’s Biographical Sketch

Brenda Curtis is a Health Communication Research Scientist at the Treatment Research Institute. Her principal research interests have been in the fields of Health Communication and Public Health with a special interest in technology. She is interested in providing scientifically tailored health information using new media that is evidence based.

References


recruitment tool in rectal microbicide development research. 
AIDS and Behavior, 1-5.


B. Curtis


On January 25, 2013, the Federal Register published the Department of Health and Human Services (HHS) omnibus amendments to the Health Insurance Portability and Accountability Act (HIPAA) Privacy, Security, Enforcement, and Breach Notification Rules. These modifications also include the final versions of the HIPAA regulation amendments mandated by the Health Information Technology for Economic and Clinical Health Act (HITECH Act) and the Genetic Information Nondiscrimination Act (GINA). Although the amended rules were effective on March 26, 2013, covered entities and their business associates (which now have direct liability for violations of the regulations) have a compliance date of September 23, 2013.

It has been 10 years since the April 14, 2003 compliance date for the original HIPAA Privacy Rule. Despite HHS’ clarification of some issues by posting answers to frequently asked questions (FAQs), there have been no significant amendments to the Privacy Rule since 2003. It has been the view of many covered entities, regulators, and analysts that several provisions of the original Privacy Rule were unworkable or caused unintended consequences. Therefore, the recent rulemaking provided an opportunity to correct some long-identified problems and to integrate congressional directives under the HITECH Act and GINA into the Privacy, Security, Enforcement, and Breach Notification Rules.

The amendments and the regulatory explanations are long, technical, and arcane. This article focuses on two important areas of the Privacy Rule with significant changes: research and genetic information. It indicates how a number of the revisions have failed to resolve or have exacerbated problems under the Privacy Rule.

### Research

**Sale of Protected Health Information (PHI)**

Based on language in the HITECH Act, the revised Privacy Rule prohibits the sale of protected health information (PHI) without an authorization. One important exception permits payment for research disclosures where the payment is “a reasonable cost-based fee to cover the cost to prepare and transmit the protected health information.” This means that the covered entity may be compensated by a sponsor for performing research; only the disclosure of PHI associated with the research is subject to this limitation.

**Compound Authorizations**

A compound authorization, which purports to authorize more than one type of use or disclosure of PHI, is prohibited by the Privacy Rule. An exception is for clinical research, where it is permissible to have a compound authorization permitting a covered entity to use or disclose PHI in treatment as part of research as well as to store an individual’s specimens for research. The authorization, however, must be clear. Clinical research also is an exception to the rule that it is impermissible to condition health care on the individual signing an authorization, including an authorization for use and disclosure of PHI in research.

**Authorizations for Future Research**

Under the Federal Policy for the Protection of Human Subjects (Common Rule), it is permissible for a research subject to consent for future research without specifying the type of research. This is especially important to the development of biobanks, whose purpose is to collect samples (often linked with health records) for possible use in undetermined future research. A significant problem has been that, unlike the Common Rule,
the Privacy Rule has required that each authorization must include a description of each requested use or disclosure. In other words, a new authorization must be signed for each study.

The revised Privacy Rule now provides that authorizations do not need to be study-specific. The authorization, however, “must adequately describe such purposes such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for future research. This could include specific statements with respect to sensitive research to the extent that such research is contemplated.” There are two parts to this clarification. First, the authorization must make it clear that future research is contemplated. Second, there “could” be specific statements about sensitive research. In effect, the rule is suggesting, but not requiring, that authorizations set forth broad classifications of possible research uses, such as genetic research, cancer research, and HIV/AIDS research, and then giving the individual an option to authorize certain types of research. This is analogous to the “tiered consent” widely used under the Common Rule. The change in policy under the Privacy Rule not only facilitates biobank-enabled research, but it also harmonizes the Privacy Rule with the Common Rule in an increasingly important aspect of research.

**Authorizations for Future Health Records**

Frequently, researchers not only want access to all of an individual’s health records as of the date the authorization is signed, but they want the individual’s future health records to be automatically added to the research file or otherwise made available to the researchers. Following the above-discussed change permitting authorizations to include future research, the revised Privacy Rule now permits authorizations to include, on an indefinite basis, future health records. “We also clarify that a description of the protected health information to be used for the future research may include information collected beyond the time of the original study.”

Unlike an authorization for future research, in which an individual can decide in a general way what broad areas of research to authorize, there is no provision permitting limits based on the content of the health records. For example, an individual who signs a research authorization today might not have any sensitive information in his or her health records. In two, five, or ten years, however, the individual might have been treated for a mental illness, sexually transmitted infection, substance abuse, or some other sensitive health condition. Although the individual would have the right to withdraw from future research, it is unrealistic to expect that an individual will remember, perhaps several years later, that he or she executed an open-ended authorization for the disclosure of all future health records. In such a situation, there is a clear conflict between the goals of protecting privacy and promoting research.

Rather than having an authorization for an unlimited time, now permitted by the revised Privacy Rule, a better approach would be to have a time-limited authorization for future health records. I have previously suggested that five years would fairly balance the interests of individuals and researchers. Thus, a new authorization for the use and disclosure of current and future health records would need to be executed every five years. Unless the Privacy Rule is amended to time-limit authorizations, researchers and their institutions should consider placing reasonable limits on the length of authorizations for future health records. Pressure from research subjects rather than regulatory requirements ultimately may persuade researchers and their institutions to alter their policies.

**Disclosures of Decedent Health Records for Research**

Promotion of historical research is behind a revision of the Privacy Rule for decedent health information. To illustrate the issue, assume that a letter written by Abraham Lincoln, in which he disclosed some of his health information, is discovered in a desk drawer in an antique shop (not a HIPAA-covered entity). There would be no prohibition under the original Privacy Rule on using and disclosing the letter, such as by sharing it with historians or publishing the contents. If the same letter were discovered in the library of a medical school, however, because a medical school is a covered entity under the Privacy Rule, the letter could not be shared with an historian because the original Privacy Rule provided that decedent health information is subject to the same protections as the health information of a living person.

The revised Privacy Rule attempts to resolve the dual problems of unequal treatment (for covered entities versus other possessors of health information) and impeding historical research by providing that protections apply only for 50 years after the death of an individual. The explanation for the amendment notes that the 50-year recommendation was made at a 2005 hearing of the National Committee on Vital and
Health Statistics (NCVHS), the federal advisory committee to the Secretary of HHS on health information policy. As a former member of the NCVHS and then-Chairman of its Subcommittee on Privacy and Confidentiality, I chaired this hearing, and the 50-year rule was based on my recommendation. My actual recommendation, however, differed from what was attributed to the NCVHS hearing and incorporated into the revised Privacy Rule. I recommended that clinical records should continue to be protected indefinitely, but “incidental” health information, such as the hypothetical Abraham Lincoln letter, would lose protection 50 years after the death of the individual.

Providing unlimited protection for clinical records respects the privacy and confidentiality interests of the decedent and the decedent’s family. It is also consistent with the AMA Code of Medical Ethics. “All medically related confidences disclosed by a patient to a physician and information contained within a deceased patient’s medical record, including information entered post-mortem, should be kept confidential to the greatest degree possible.” The revised Privacy Rule fails to balance the interests at stake by not distinguishing between clinical records and incidental health information.

Genetic Information
The revised Privacy Rule contains several provisions dealing with the application of genetic information, as mandated by GINA. Three of the most important provisions are described below.

Use of Genetic Information for Underwriting in Long-Term Care Insurance
GINA requires the Secretary of HHS to modify the Privacy Rule to prohibit a covered entity that is a group health plan, health insurance issuer, or issuer of Medicare supplemental policies from “using or disclosing genetic information for underwriting purposes.” As applied to traditional health insurance, the provision is consistent with the primary congressional purpose behind Title I of GINA, prohibiting “genetic discrimination” in health insurance. The original Privacy Rule, however, included within the definition of “health plan” long-term care insurance policies. Thus, the important question was whether long-term care insurance companies would be prohibited by the Privacy Rule from using genetic information in underwriting.

The answer to this question is especially important in light of new genetic studies identifying genetic factors associated with Alzheimer’s disease. Because the cost of skilled nursing care for individuals with Alzheimer’s disease is significantly higher than for the less intensive care for other recipients of long-term care services, the Privacy Rule determination has major implications for long-term care insurers, individual purchasers of long-term care policies, and the public (because of the consequences for publically-funded nursing home care under Medicaid).

Unlike the provision in the Notice of Proposed Rulemaking, the final Privacy Rule exempted long-term care insurance from the prohibition of using or disclosing genetic information for underwriting purposes. The final rule is faithful to the legislative history of GINA, which indicates the intent to exclude long-term care insurance, as well as life and disability insurance, from coverage. Nevertheless, a compelling public policy argument could be made that broadly underwritten and widely available private long-term care insurance should be encouraged, and therefore underwriting based on genetic factors should be prohibited. The responsibility for adopting such a policy change, however, belongs to Congress or state legislatures rather than HHS under the Privacy Rule.

Definition of “Manifestation”
GINA only prohibits discrimination based on genetic information about an individual at the presymptomatic stage. By statute, genetic information includes the individual’s genetic test results, the genetic test results of a family member, or the health history of a family member. GINA does not apply to health conditions that have “manifested,” which the revised Privacy Rule defines to mean “that an individual has been or could be diagnosed with the disease, disorder, or pathological condition by a health care provider with appropriate training and expertise in the field of medicine involved.”

Recent scientific developments indicate that it is simplistic or even inaccurate to use a bimodal approach to genetic, as opposed to nongenetic, factors in the etiology of disease. As scientists have learned more about the processes by which genotype becomes expressed as a disease phenotype, it is increasingly clear there are several intermediate steps. It is quite likely, however, that these biomarkers, protein expression profiles, epigenetic marks, endophenotypes, and preliminary symptoms would be considered “manifestations” of disease under GINA because these discrete markers extend beyond health risk factors based on genetic information. If these intermediate biological conditions are considered “manifestations,” then discrimination based on such markers would not be prohibited by GINA. At the same time, minor biological precursors of possible future disease are insufficiently severe or definite to trigger protection for the affected individual under the Americans with Disabilities Act (ADA).

It can be argued that the GINA framework for coverage is frozen in the state of the art of genetics in the 1990s and needs to be revised to afford individuals seamless protection against discrimination at any point in the disease-development process. Unfortunately, the revised HIPAA Privacy Rule has reinforced the GINA framework, thereby extending the coverage gap to newly discovered types of health information.

Disclosure of Genetic Information with Health Care Providers of Family Members
According to an interpretation of the revised Privacy Rule, “health care providers may share genetic information about an individual with providers treating family members of the
individual who are seeking to identify their own genetic risks, provided the individual has not agreed to a restriction on such disclosure.29 The disclosure, however, is “subject to the individual's agreement.”30 This interpretation is at variance with established principles of medical ethics and should be ignored by health care providers until a better reasoned interpretation is developed by HHS.

A physician or other health care provider who learns genetic information about a patient that may be valuable to a patient’s biological relatives should encourage the patient to notify at-risk family members or to authorize the physician to contact the family members or health care providers of the family members. Therefore, the HHS interpretation assumes the patient has expressly declined to notify his or her relatives or to authorize disclosure by his or her physician. The interpretation provides that health care providers may disregard the wishes of their patients and notify relatives over their patient’s objection. The “agreed-upon restriction” language would require both patient and physician to agree and, by definition, in this situation there is no agreement.

This interpretation of the revised Privacy Rule undermines the physician-patient relationship and contradicts authoritative codes of medical ethics. Section 2.131 of the AMA Code of Medical Ethics, Disclosure of Familial Risk in Genetic Testing, provides that “Physicians have a professional duty to protect the confidentiality of their patients' medical information, including genetic information.”30 In addition, the American Society of Human Genetics details the “exceptional circumstances” that would permit physician disclosure to at-risk relatives. Disclosure is only permissible when “attempts to encourage disclosure on the part of the patient have failed; the harm is highly likely to occur and is serious, imminent, and foreseeable; the at-risk relative(s) is identifiable; and the disease is preventable, treatable, or medically accepted standards indicate that early monitoring will reduce the genetic risk.”31 The HHS interpretation sets an unreasonably low standard for disclosing genetic information over the objection of a patient.

Conclusion
The revised Privacy Rule makes numerous changes mandated by the HITECH Act and GINA, as well as modifications suggested by a decade of experience in enforcing the Privacy Rule. Two of the most important areas addressed by the revised Privacy Rule are research and genetics. Regrettably, some of the revisions related to these concerns are among the least well considered. In attempting to limit burdens on researchers, the revised Privacy Rule permits authorizations to include all future-developed health information without any time restriction. It also limits all protections on decedent health information to 50 years after the death of the decedent. Many of the problems of inadequate privacy protection for genetic information stem from the limitations of GINA, which have been reinforced by the revised Privacy Rule. One such interpretation of the revised Privacy Rule unwisely permits disclosure of genetic information to at-risk family members by a physician over the objection of his or her own patient, thereby directly contravening established principles of medical ethics.

References
5. 45 C.F.R. § 164.534 (2002).
7. 45 C.F.R. § 164.502(a)(5)(ii).
8. Id.
10. 45 C.F.R. Part 46, Subpart A.
11. 45 C.F.R. § 46.116.
12. 45 C.F.R. § 164.508(b)(3).
16. 45 C.F.R. § 164.502(f) (2003). It should be noted that only living individuals may be research subjects under the Common Rule and therefore there is no prohibition on the use of the records for research.
21. GINA § 105.
23. 45 C.F.R. § 164.502(a).
25. GINA § 102(a)(4).
29. Id.
Critics of the institutional review board system have argued that research has changed, whereas the structure of the institutional review board has not. Institutional review boards were formed to ensure the critical ethical, regulatory, and scientific oversight of human subject research. Compared to when the boards were formed, there is now more clinical research and more research involving multiple, collaborating sites, some of which may be international. Others have raised concerns that board members are burdened with work, including the review of minimal risk research. The Institute of Medicine was commissioned to assess the national system for human subject protection in research. They found that “dissatisfaction with the current system is widespread.” Although waiting for institutional review board approval can be bothersome, the importance of the question is more than that. There must be a balance between protecting human research subjects without hindering the progress of research. The purposes of this article are to review the history, structure, and purpose of the institutional review board, to assess the criticisms of the current system, and to discuss solutions for improvement.

**HISTORY**

A history of the major events to enforce protections for human subjects in research is provided in Table 1. Before 1991 and the adoption of the Common Rule (which documents the requirements for institutional review boards), federal departments and agencies involved with human subject research used a variety of policies and procedures to protect subjects. Institutional review boards have jurisdiction over “all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency.” Definitions of commonly used terms are included in Table 2.

The composition of an institutional review board is mandated by federal policy. Institutional review boards are required to have at least five members with varying backgrounds to provide adequate review of the types of research commonly conducted by an institution. They must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. It must also include at least one member who is not otherwise affiliated with the institution (drawn from the local community and knowledgeable about that community). An investigator can be an institutional review board member, but he or she cannot participate in the review and approval process for any project on which he or she could have a conflict of interest. Likewise, members of the
institutional review board cannot participate in the review of any project in which there is a conflict of interest. The board may not consist entirely of men or women, but selections must not be made on the basis of gender. An institution may have more than one institutional review board. Although the board may work in coordination with other research committees, such as those that determine whether an institution should support the proposed research, it functions independently to determine whether or not to approve of a research protocol based on whether or not human subjects are adequately protected. Board members may be paid for their time and expenses to attend the meetings.4

The main job of the institutional review board is to protect human subjects. Federal regulations do not require boards to review the scientific validity of the research design, but they do require that subject risks are reasonable in relation to the importance of the knowledge that may result. Thus, generalizable knowledge is not likely to result from a poorly conceived study.3 If subjects have been exposed to risk or have volunteered their time for a study that does not produce any useful data, the study is unethical.1 Rigorous review of the science is usually left to the funding agency’s peer review process.3 However, when a study does not have federal funding, the scientific review may be provided by a review from an internal funding source. The Institute of Medicine states, “Scientific review of a protocol should be particularly rigorous at the local level

### Table 1. History of Human Subjects Protections*

<table>
<thead>
<tr>
<th>Year</th>
<th>Act</th>
<th>What It Did</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Nuremberg Code</td>
<td>Developed basic principles governing the ethical conduct of human subject research.</td>
</tr>
<tr>
<td>1964</td>
<td>Declaration of Helsinki</td>
<td>Provided recommendations to guide medical doctors in biomedical research involving human subjects. Further distinguishes therapeutic from nontherapeutic research.</td>
</tr>
<tr>
<td>1974</td>
<td>National Research Act</td>
<td>Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). The Commission identified basic ethical principles for human subject research and developed guidelines to ensure that research is conducted in accordance with these principles.</td>
</tr>
<tr>
<td>1979</td>
<td>Belmont Report</td>
<td>Identified three fundamental ethical principles for all human subject research: respect for persons, beneficence, and justice.</td>
</tr>
<tr>
<td>1991</td>
<td>Federal Policy for the Protection of Human Subjects (Common Rule)</td>
<td>A uniform set of rules for the protection of human subjects was adopted by federal departments. The Common Rule requires that federally funded investigators obtain and document informed consent and describes the requirements for institutional review boards.</td>
</tr>
</tbody>
</table>


### Table 2. Commonly Used Terms and Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>“A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”</td>
</tr>
<tr>
<td>Human subjects</td>
<td>“Living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.”</td>
</tr>
<tr>
<td>Minimal risk</td>
<td>“Where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”</td>
</tr>
<tr>
<td>Adverse event</td>
<td>“Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical examination or laboratory finding), symptom, or disease, temporarily associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.”</td>
</tr>
<tr>
<td>Unanticipated problem</td>
<td>“Any incident, experience, or outcome that meets all of the following criteria: (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; (2) related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.”</td>
</tr>
</tbody>
</table>

IRB, institutional review board.
if the study will not be submitted for federal funding and/or will not be subjected to a peer review process similar to that of the National Institutes of Health or the National Science Foundation."1

Sometimes the board has limited understanding of the research that is being proposed, causing it to be unapproved. This often leads to frustrations for the research investigator. The Institute of Medicine recommends that the board be restructured to focus on ethics review and be renamed "Research ERB" (research ethics review board). Scientific and financial conflicts of review would be completed by separate divisions and then “feed into” the research ethics review board’s comprehensive review.6

Unfortunately, lapses in human subject protection have resulted in dire consequences. In 2001, a young, healthy research subject died at Johns Hopkins University. The research subject died a month after inhaling an unapproved drug as part of a research study to examine the causes of asthma. As a result, a federal oversight agency suspended almost all of the university’s federally funded human subjects research.5 Although the institutional review board can be blamed for tragedies such as this, the ultimate responsibility for ensuring patient safety lies with the primary investigator. Proper enrollment, reporting of adverse events, and study monitoring are the responsibilities of an ethical investigator.6

CRITICISMS OF THE CURRENT SYSTEM

There has been an explosion in the workload of institutional review boards since their formation. One reason is because over the past few years, the number of clinical research studies has increased by leaps and bounds. As of May of 2013, there were more than 146,000 clinical trials registered on ClinicalTrials.gov.7 This number is up from 5645 studies that were registered in 2000, when the Web site debuted. “Applicable clinical trials” that are required to register for this site include interventional studies of Food and Drug Administration–regulated drugs, biological products, or devices. Other studies may voluntarily register, and registration of clinical trials in some type of public registry has become a requirement for publication by the International Committee of Medical Journal Editors.8 Although the increase in registered clinical trials over time is due to new registration requirements, there has undoubt edly been an increase in the number of trials conducted. Total spending on health-related research and development by pharmaceutical companies and the federal government is estimated to have tripled since 1990.9 This increase translates into an increase in the workload for institutional review boards.

Critics of the institutional review board system argue that the bureaucratic procedures of the board consume resources of time and money without translating into better human subject protection. One investigator stated, “The [institutional review board], with all its work, dreams up corrections.”10 Similarly, one editorial stated, “[Institutional review board] members spend too much time editing documents, marking typos, and asking for more details.”11 Research may be hindered if time is lost because the board is focusing on issues that are unrelated to human subject protection. Also, the public may not be willing to participate if they do not feel adequately protected.12 If the available study sample is reduced or otherwise biased, especially because of differences in consent forms among study sites, this can reduce the likelihood of a study producing meaningful results, which also reduces its ethical integrity.13

Other causes of increased institutional review board workload include the requirement that continuing review of protocols and most amendments are conducted in fully convened board meetings. On July 26, 2011, the U.S. Department of Health and Human Services issued an advance notice of proposed rulemaking to revise and strengthen the regulations for protecting human research subjects.14 The notice was opened to comments but has not yet been finalized. One reform proposal under this notice is to eliminate continuing review for all minimal risk studies that underwent expedited review, unless there is a need for continuing review to protect the subjects. Similarly, the notice recommends eliminating continuing review for studies that were initially reviewed by a convened institutional review board once the study reaches the data analysis stage or is accessing clinical data from procedures that are part of a subject’s standard care.

Another reason for increased workload is that institutional review boards are required to monitor adverse events. Unfortunately, there is no common definition of an adverse event, but a broad definition is provided in Table 2. Furthermore, investigators have to identify whether the adverse event is an unanticipated problem (also defined in Table 2). Figure 1 shows a flow diagram to determine whether an adverse event is an unanticipated problem (the majority are not). Some feel that the responsibility for reporting should
be shifted from institutional review boards to data monitoring committees or data and safety monitoring boards.\textsuperscript{11,13,16} Data monitoring committees are generally groups of individuals who are appointed to a clinical trial by a sponsor and have pertinent expertise. The committee reviews the accumulating data on a regular basis and advises the sponsor on the safety of the recruited subjects and those yet to be recruited, as well as the validity and scientific merit of the trial.\textsuperscript{17} Although there may be multiple institutional review boards in a multisite study, there is only one data monitoring committee. In our 21-site study, Wrist and Radius Injury Surgical Trial,\textsuperscript{18} a six-member data and safety monitoring board was appointed by the funding agency, the National Institutes of Health. This data and safety monitoring board consists of a biostatistician, three orthopedic surgeons, and a gerontologist/clinical trialist (this study is restricted to patients 60 years and older). One member serves as the chairperson and one other member serves as the safety officer. Monthly reports are submitted by the coordinating site to the data and safety monitoring board that summarize the current and projected enrollment, patient demographics, missing visits or data, protocol deviations, and adverse events overall and by site. The group meets every 6 months to review the reports. Serious adverse events, such as deaths, are immediately reported to the site-specific institutional review board as well as to the data and safety monitoring board. Currently, investigators

\textbf{Fig. 1.} Reporting guidelines for adverse events/unanticipated problems. Adapted from U.S. Department of Health & Human Services, Food and Drug Administration. Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. 2007. Available at: http://www.hhs.gov/ohrp/policy/advevntguid.html. Accessed June 6, 2013.
often have to submit adverse event reports to multiple agencies: the local institutional review board, the data monitoring committee (if applicable), and the sponsor. The Department for Health and Human Services states, “... most [institutional review board] members, investigators, and institutional officials understand the scope and meaning of the term adverse event in the research context, but lack a clear understanding of ... what, when, and to whom adverse events need to be reported as unanticipated problems.” Health and Human Services has proposed a single Web site for electronic reporting that would decrease administrative burdens and enhance the ability to identify and respond to risks from research interventions. The Institute of Medicine proposes that the definition of an adverse event, the reporting format, the report recipients, and reporting timelines all be clarified and harmonized among federal agencies in order to enhance compliance. Furthermore, the Institute recommends ongoing continuing education programs for clinical investigators, with specific instructions about assigning a causal relationship of the adverse event to the drug, biologic, or device under investigation. Clinical trial participants also need education on how to recognize and report adverse events to the study personnel. To effectively protect study participants, the data monitoring committee must advise the institutional review board as to whether new adverse event information affects the safety of participants, and if so, that the information needs to be conveyed to the participants.

Improvements in collaboration, including studies with multicenter and international partnerships, have increased the complexity of institutional review board regulation. On ClinicalTrials.gov, 6 percent of the registered studies have locations in both the United States and non–United States. In these studies, each participating institution must obtain institutional review board approval, which also means that each site has its own informed consent document. One study found that after local review of the informed consent document in a multicenter trial, some sites required minimal changes whereas others required up to 160 changes. In our Wrist and Radius Injury Surgical Trial involving 21 study sites, the coordinating center’s institutional review board had to reach a final opinion on all study items before the other sites could initiate their institutional review board application. The data and safety monitoring board required the inclusion of certain documents before institutional review board approval at the coordinating center was complete. Because of these delays, it took nearly a year for some sites to obtain institutional review board approval. Some institutional review boards in the Wrist and Radius Injury Surgical Trial study required that the site have two consent forms (one for patients in the surgical study arm and one for patients in the nonsurgical study arm), while other sites only have one consent form for both study arms. In general, the concerns of one institutional review board are not necessarily relayed to the boards at the other participating sites. This can affect the protection of human subjects as well as the decision of subjects to enroll in the study, depending on the wording of the informed consent document. Differing subject enrollment at each study site can lead to biases in the sample, reducing the likelihood that the study will produce quality results. The Institute of Medicine stated that the variability produced by duplicative review of multicenter protocols may actually detract from human subject protection. Many have proposed using a centralized institutional review board system. The National Cancer Institute, in consultation with the Department of Health and Human Services Office for Human Research Protections, has created a Central Institutional Review Board Initiative of multicenter cancer treatment trials. This process reduces the workload of local institutional review boards but still retains their authority to accept or reject the review provided by the Central Institutional Review Board. Local boards need to comply with the Office for Human Research Protections guidance that if institution A relies on institution B for institutional review board review, institution A still has the responsibility of ensuring that local research policies are being upheld. This is done by subsequent review by a designated official at institution A. A centralized board can also reduce the possibility of having a conflict of interest because the board’s members are not at the same institution as the investigator. Similar to the Central Institutional Review Board, a collaborative review model called IRBshare has been created. IRBshare uses a centralized, secure Web portal to house the institutional review board documents in a multicenter study. The participating institutions can also have a shared review process, if they wish, whereby they rely on one full board review and then complete their own shared review (via a subcommittee) to address local issues. Participating institutions can also undergo a full review if they choose not to use a shared review. All post-approval documents (continuing review, local adverse events, amendments, and so on) will be reviewed locally. The Office for Human Research
Protections has acknowledged that IRBshare is permissible under their regulations. Dr. Robert J. Levine, from the Yale University School of Medicine, states in an editorial that he would add an educational system for institutional review board staff and members followed by an accreditation system for boards and certification system for the staff. The Institute of Medicine’s recommendations are similar. They recommend that the Office for Human Research Protections engages representatives to develop practical guides for risk classification. Because some institutional review boards are afraid of being noncompliant with federal guidelines, they are often too strict and do not allow exemptions from review or inconsistently allow for expedited review. The Institute of Medicine states, “Review boards lack clear guidance about how to make these assessments and do not have sufficient educational materials available to assist in these determinations, which are key to ensuring adequate levels of protection.” Educational resources provided by the Department of Health and Human Services include training videos, webinars, conferences, and a quality assessment program. Public Responsibility in Medicine and Research is an organization dedicated to advancing the highest ethical standards in research through educational and professional development. They offer certification for institutional review board staff and members, and they recommend that the Office for Human Research Protections engages representatives to develop practical guides for risk classification.

Human subjects are a valuable resource and their safety must be protected. Although it is easy to try to place any failures in the system on the institutional review board, there are multiple areas for improvement. One must remember that board members aim to protect the welfare of human subjects, and criticism will not improve their morale or help them to try to place any failures in the system on the institutional review board. Research has changed dramatically since the introduction of the institutional review board, and it may be beneficial to all parties to reevaluate the current system to determine whether certain concerns can be handled better by other agencies and/or by collaborations with the institutional review boards.

ACKNOWLEDGMENT

This work was supported in part by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging (R01 AR062066) and from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR047328), and by a Midcareer Investigator Award in Patient-Oriented Research (K24 AR053120) to Dr. Kevin C. Chung.

REFERENCES


**PRS Mission Statement**

The goal of Plastic and Reconstructive Surgery® is to inform readers about significant developments in all areas related to reconstructive and cosmetic surgery. Significant papers on any aspect of plastic surgery—original clinical or laboratory research, operative procedures, comprehensive reviews, cosmetic surgery—as well as selected ideas and innovations, letters, case reports, and announcements of educational courses, meetings, and symposia are invited for publication.