IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

December 2010: Vol. 10, No. 12
Pages 133-144

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Statement of Financial Disclosure: Editor Suzanne Koziatek, Editor Melinda Young, Executive Editor Coles McKagen, Senior Managing Editor Gary Evans, Nurse Planner Kay Ball, and Physician Reviewer Mark Schreiner, MD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies related to the content in this CNE/CME activity.

Guatemalan research travesty raises new questions for IRBs

'Worse than Tuskegee — these people were deliberately infected'

The recent shocking disclosure that U.S. public health officials sanctioned a study in Guatemala 64 years ago in which people were deliberately infected with sexually-transmitted diseases (STDs) for research purposes has brought home the message to IRBs that transparency is absolutely critical in human subjects research.

Top U.S. officials were quick to offer public apologies to Guatemala in October, 2010, after an historian found evidence that the U.S. Public Health Service was involved in experiments between 1946 and 1948 in which Guatemalan men and women were infected with syphilis or other STDs without their knowledge.

The shocking disclosure was eerily reminiscent of the Tuskegee syphilis study, and even more alarming was the announcement that one of the Guatemala study's investigators, John Charles Cutler, MD, was also involved in the Tuskegee research. Cutler died in 2003.

"The real issue here is that these communities were not treated as people in their own right," says **James Lavery**, MSc, PhD, a research scientist at St. Michael's Hospital in Toronto, Canada.

IRB and research officials find news of the Guatemalan study particularly disturbing because of its focus on using vulnerable populations without any sort of informed consent during an experiment in which they were deliberately and covertly infected.

"One of the sentinel events in the human subjects research history was the Tuskegee study, and this one seems worse than Tuskegee because these people were deliberately infected," says **Brenda L. Ruotolo**, CIP, associate director of the Columbia University IRB office in New York, NY.

"We went outside our country to find a convenient sample of people who were not capable of providing consent," she adds. "They were educationally-disadvantaged and more vulnerable than the average person."

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Tuskegee parallels

The U.S. Public Health Service studied the effects of syphilis on African-American men from 1932 to 1972 at Macon County, AL, near Tuskegee. The men were examined regularly as part of the study, but they were never given treatment, even after 1947 when penicillin was widely accepted as a cure for the disease. In 1972, media reports and public outcry about the Tuskegee Syphilis Study led to the 1979 Belmont Report, the requirement of institutional review boards and the establishment of a federal office that oversees human subjects research. President Bill Clinton publicly apologized in 1997 to the surviving Tuskegee men who were subjects of the study.

The parallels to the Guatemalan study are disturbing: in the Guatemalan study, hundreds of prisoners, soldiers, and people with mental illness were intentionally infected with syphilis between 1946 and 1948. The research goal was to determine if a new antibiotic could prevent infection after exposure to the diseases, but the study ended without answering the question. A Wellesley College historian Susan Reverby discovered archives of the study and brought it to public attention. Secretary of State Hillary Clinton and Secretary of Health and Human Services Kathleen Sebelius both denounced the research in recent public statements.

One of the more troubling aspects of the Guatemalan study is that it took place during the time period in which the world was learning of the war crimes of Karl Brandt, Adolf Hitler's personal physician, who was convicted in 1947 at the Nuremberg trials for medical experimentation crimes. The result of that conviction was the Nuremberg Code, which has 10 principles with the first stating, "The voluntary consent of the human subject is absolutely essential."

While no IRB will want to compare the exploits of Nazi scientists with research conducted by U.S. researchers, the Guatemalan study demonstrates that breaches of research ethics can occur even in a nation that prides itself on respecting human rights.

"To me, the Guatemalan study story is a reminder that the rules and what we think of as standards in these are very far from self-executing," says **Alex Capron**, a professor at the University of Southern California in Los Angeles, CA. Capron also is a professor of law and medicine at the Keck School of Medicine, and he's the Scott H. Bice Chair in Healthcare Law, Policy and Ethics and co-director of the Pacific Center for Health Policy and Ethics.

"Here you have people who were doing the work they were doing in a very brief period after the Nuremberg decision had been handed down and the Nuremberg Code created," he adds.

IRB Advisor (ISSN 1535-2064) is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to IRB Advisor, P.O. Box 740059, Atlanta, GA 30374.

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Editors: **Suzanne Koziatek and Melinda Young**.
Executive Editor: **Coles McKagen**, (404) 262-5420 (coles.mckagen@ahcmedia.com).
Senior Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Neill L. Kimball.**

Editorial Questions

Questions or comments?
Call Gary Evans at (706) 310-1727.

It's possible Cutler and other investigators involved in the Guatemalan study were unaware of the Nuremberg trial. Another researcher, Chester M. Southam, who in 1962 had injected cancer cells into 22 elderly patients at the Jewish Chronic Disease Hospital in Brooklyn, NY, had confessed to being unaware of the Nuremberg Code when he was up before the Board of Regents in New York for having his license suspended, Capron notes.

"Southam had a lot of prominent witnesses who testified in his defense that the practice of not telling people the truth of what you were doing in research was common practice," Capron says.

"He didn't want to tell patients he was injecting cancer cells into them because of the great fear and phobia about cancer," he adds. "So Southam rationalized that you don't tell people what you are putting in them because they'll be unduly upset, and that's more or less what was going on with Cutler in Guatemala."

The Guatemalan study disclosure brings home the point that this grievously unethical research was not some privately-funded, rogue endeavor, but an investigation sponsored by the U.S. government, Lavery says.

"People do beautiful deflection when they talk about the Tuskegee trials, which takes away from the U.S. government's stain of involvement," he adds. "But like Tuskegee, this study was a program of the U.S. Public Health Service; these were not rogue investigators."

The U.S. government's role in the study makes it even more imperative that IRBs and researchers address this 64-year-old ethical breach and make certain that today's research subjects know that safeguards are in place to prevent anything like this from happening again, experts say.

Be proactive on education

At least one IRB had discussed the Guatemalan study within a week of its announcement.

The IRB at LeHigh Valley Health Network in Allentown, PA, discussed the news at an October IRB meeting, says **Scott J. Lipkin**, DPM, CIP, an associate vice president of research for LeHigh Valley Health Network. *(See story about how to update IRB education, p. 136.)*

"It's kind of mind-boggling that this is just being uncovered now," Lipkin says. "I'm assuming that public outcry would have been just as vast and immense as what happened with Tuskegee if people had known about this back then."

IRBs need to think about how to incorporate this latest example of unethical research in their educational and training materials for new members.

"I've already updated my slides," Lipkin says. "I put this in a section after Nuremburg and before Tuskegee — basically bulleting the facts on the slide."

When the Guatemalan study is discussed with new IRB members, it's important to note that this experiment was not known by the general research community and the public until this year, he adds.

"We should explain that the regulations were written as a result of Tuskegee and not Guatemala," he says.

Experts say they are uncertain how much fallout will occur as a result of the Guatemalan study disclosure.

"It underscores the need for regulations," Ruotolo notes. "We assume people will do the right thing, but the right thing is different to different people."

When the public hears even dated comments, such as those reportedly made by Cutler about the Guatemalan experiments, that there are different rules for research, then this can create problems for researchers and IRBs.

"It can feed into the problem of how lay people understand research," Ruotolo says. "At Columbia, we are a major academic research institution that sits in the middle of a densely populated area, and our local population overall has a lack of balanced information about research."

The Columbia University area has populations of Spanish-speaking individuals, including people who are economically disadvantaged, and some of them might be hesitant to enroll in trials out of concern of being used like a guinea pig, she notes.

However, these same populations could find some benefits from being in the proximity of a major research institution, an opportunity that is not widely available to disadvantaged populations, she adds.

"We have an obligation to the community to get out there and provide the other side of it," Ruotolo adds. "People should be informed so they can make a decision, but they shouldn't write off all research participation." ■

Boost education in light of Guatemala revelation

Could fuel more distrust of researchers

IRB members and research offices need to add the Guatemalan experiment to their human subjects research training and redouble efforts to educate the public about the high level of ethics and protections in research projects today, experts say.

"Among my IRB members there is a very high level of comfort in the work we're doing to protect human subjects and that our efforts and measures are effective," says **Scott J. Lipkin**, DPM, CIP, an associate vice president of research for LeHigh Valley Health Network in Allentown, PA.

The research office is accredited and works hard to improve communication with subjects, putting in place a venue for complaints, he adds.

But without transparency these efforts might not be enough, especially when the public learns of another dark chapter in U.S. human subjects research.

"This news of the Guatemalan study doesn't change anything in the present or cause us to lose credibility about our current protections," Lipkin notes. "But it does mean we should add another layer of education."

Research institutions have a responsibility to get balanced information out to the community, says **Brenda L. Ruotolo**, CIP, associate director of the Columbia University IRB office in New York, NY.

"We've developed brochures about questions people should ask about research," she says. "And in New York, there are citizen groups that speak for the community and identify issues, and we work with them."

News of the Guatemalan episode might feed into existing community concerns and distrust, she notes.

"We have to make sure people are informed about how research is conducted because when something like this comes out it raises valid issues," Ruotolo adds. "From the IRB point of view, it's the reason why we're such sticklers."

For instance, it can be a burden for researchers and a research site to make certain they have good communication practices in place, including having informed consent forms and educational materials translated into different languages. But this is an important part of the IRB review, Ruotolo says.

This latest chapter in the darker history of human subjects research is a reminder of the fundamental issues that IRBs need to keep in mind, says **Alex Capron**, a professor at the University of Southern California in Los Angeles, CA. Capron also is a professor of law and medicine at the Keck School of Medicine, and he's the Scott H. Bice Chair in Healthcare Law, Policy and Ethics and co-director of the Pacific Center for Health Policy and Ethics.

While it's difficult to imagine 21st century research being conducted in as outrageous a manner as what happened six decades ago, it is important for IRBs to worry about ethnic and economic vulnerability among the populations being studied, he adds.

For instance, IRBs should make certain subjects' education and informed consent are clear and simply conveyed.

"IRBs need to make sure that not just the minutia of details, but also the basic frameworks is conveyed to subjects," Capron says. "Tell them they are being asked to enroll in a study because of the benefit to science."

One of the economic vulnerabilities today is that many people will enroll in research because of their need for some kind of health care. This puts them in a position of not freely making a decision, he explains.

Research subjects often are in a situation in which they are volunteering for a study because they don't have other financial or medical prospects, he adds.

"Because of a disability they might not make fully rational and informed decisions," Capron says. "The standard informed consent language says you can withdraw from the study at any time and it will not affect the care you receive, but of course that is false if the only care you receive is in the study."

The goal would be to create a power relationship that puts investigators and subjects on equal footing — a collaboration, he adds.

One way to move toward that objective is to add an extra page to the informed consent form with one sentence in large type at the top of the page, saying that this study is an experiment and not treatment, Capron suggests.

"Let's be clear about what we're talking about here," he says. "It's noble to be in research, but it's not noble if you don't know what you're doing." ■

Ethical issues arise with research on Internet

How should IRBs handle virtual worlds?

One of the strangest new areas of research ethics involves how IRBs should handle research that involves Internet communities, including virtual communities.

IRBs have some experience and background in handling online surveys or assessing protocols that involve the collection of data available over the World Wide Web. But what do they do when an investigator proposes to visit an online world to study the community as an avatar?

"There are people behind these avatars, and a lot of times researchers are not that sure about who they need to obtain consent from," says **Montana Miller**, PhD, an assistant professor at the Bowling Green State University in Bowling Green, OH.

For instance, there's an online world called Second Life in which people can create a person who has a job, house, family, and friends. Some visitors will spend hours in this imaginary community, closely identifying themselves with their avatar.

"A lot of researchers feel it's too daunting to even try to get informed consent so they will avoid the whole issue and convince themselves it's just an avatar and not a person so it's not human subjects research," Miller says. "And sometimes even an IRB is confused and says it's not human subjects research."

But the ethical reality is more nuanced. Virtual worlds like Second Life advertise themselves to be places for people to connect, explore, have adventures, and find love. While a researcher might be detached when visiting these communities, chances are that other people are more personally engaged in the recreational activity.

"It may not seem like you're studying a person because you're looking at a computer screen," Miller explains. "However, research shows that when you do something to someone online, whether it's to support or bully them or some other interaction, then what happens on that computer screen has a real effect on the person behind that computer screen."

IRBs and investigators should keep in mind that these virtual avatars represent real people, real feelings and real harms, she adds.

"Strangely enough, that is something researchers seem to forget or ignore," Miller says. "Even when you're typing things out through text or even when it doesn't feel real, it may feel real to them."

Studies show that when someone's avatar is hurt, the person also feels that pain emotionally, she adds.

It's similar to the experience of "flaming" someone online, Miller says.

Internet flaming refers to deliberate acts of posting messages online with the intent of insulting and creating havoc with specific people or groups. Sometimes this act can be personal and a form of bullying, and sometimes it's meant to be provocative and directed at a general group or community.

"Flaming someone is unprovoked and nasty attacks that can make someone feel absolutely terrible," Miller explains. "You'd think, 'Why am I so upset when I don't even know this person?' But it really does have an emotional effect."

Here is how a researcher might unknowingly cause someone similar emotional distress: "Suppose you do an experiment where someone walks up to a person in Second Life as an avatar and has some interaction with the person. Then the researcher turns around and walks away," Miller says.

"That may seem innocent and benign, but to the person in Second Life that may be shocking or disturbing to have a stranger walk up to them and say something and then walk away," she adds. "Researchers have to take responsibility for how their behaviors as an avatar in a virtual world impact other people."

As IRBs review this type of research, they should consider how the researcher will represent himself or herself to the online community.

"This is a community of people who often are misunderstood by the general public, and there are issues of confidentiality and identity," Miller says.

For instance a researcher might decide to visit Second Life to do a study of romantic relationships. While conducting this research, the investigator sees avatars connecting in virtual love affairs with other avatars. These avatars are represented by people who have committed relationships in the real world, so their virtual affairs could be seen as cheating by their real-life partners, she explains.

"A researcher could do a study in which he or she unintentionally exposes identifying information, which could have an impact on their real lives," Miller says.

"Some researchers say they are just using the avatar's online handle or screen name so they're

not really identifying them," she adds. "But someone could track that down through all these other places on the Internet where that screen name is used, and that's why a screen name is an identity."

The key is to change the screen name or omit it entirely from the study.

"IRBs and researchers need to figure out just how rigorous the consent needs to be," Miller suggests. "In some cases it may involve actually being able to contact the real person, give the person a real consent form."

In other cases, IRBs might decide to waive written consent, but require investigators to identify themselves as researchers and provide a public information sheet to those involved in the study.

"It depends on different factors, such as whether the online community is a public or private space, and what is the topic sensitivity," Miller says. "And how much of an intervention is the investigator doing? Is the investigator just observing or is he or she asking questions and really doing an experiment involving the avatars?" ■

Websites allow studies to cast wide net for subjects

Amazon's Mechanical Turk used by researchers

Researchers go to all sorts of lengths to attract participants for surveys and other types of non-clinical research — recruiting Psych 101 students, posting fliers, handing out gift cards, etc. But a new method of recruitment takes advantage of an existing Internet trend toward outsourcing tasks to thousands of computer users around the world.

"Crowdsourcing" allows a requester to put out an open call for help with a particular task that requires human intelligence and therefore cannot be done by computer programs alone. These tasks are often mundane — tagging images with identifying information, filtering out obscene photos and comments from websites, transcribing audio to text, posting reviews.

Increasingly, however, investigators are exploring the use of crowdsourcing to cast their nets for subjects more widely than they can within the confines of their institution, or even their institutional Web sites. They do so by posting surveys and other studies on crowdsourcing sites alongside other non-research related tasks. The most popular of these sites is Amazon's Mechanical Turk, which bills itself as an open marketplace for work requiring human intelligence. (http://aws.amazon.com/mturk).

According to the account posted on the Amazon website, the name comes from a chess ruse concocted in 1769 by Hungarian nobleman Wolfgang von Kempelen, who built a mechanical chess-playing "Turk" automaton that defeated nearly every opponent it faced. Kempelen convinced people he had built a machine that made decisions using artificial intelligence, but in reality a concealed human chess master made the moves. "Humans still significantly outperform the most powerful computers at completing such simple tasks as identifying objects in photographs — something children can do even before they learn to speak," Amazon notes.

Mechanical Turk brings together workers, known as "Turkers" and "requesters." Requesters post Human Intelligence Tasks (or HITs), and Turkers fulfill them. Once the requester is satisfied with the work, he or she releases money from an account to the worker's account — usually only a few cents per task.

Amazon holds the personal information about workers in order to pay them, but does not pass them along to the requesters.

This ability to attract potentially thousands of anonymous responses for minimal cost has attracted the interest of researchers such as **Chris Callison-Burch**, PhD, an associate research professor in the computer science department at Johns Hopkins University in Baltimore.

Callison-Burch works in the field of computational linguistics, on the problem of automatically translating from one language to another. He has posted a number of HITs on Mechanical Turk asking workers to translate words and phrases from one language to another. Despite the minute cost he pays per task, he says he now spends thousands of dollars a month conducting research on it.

He calls Mechanical Turk "a really amazing tool for performing experiments."

"When you compare it to the experiments I encountered in my undergraduate days – such as taking psychology classes and being roped into being a subject for grad students, the scale at which you can do these is much, much larger."

New to IRBs

Terrell Russell, MS, a PhD student and research assistant at the School of Information and Library Science at the University of North Carolina at

Chapel Hill, is likewise a convert to the greater efficiency of using Mechanical Turk for research.

"It's cheaper — and it's way faster," he says. "I don't have to have them come into the lab. I don't have to talk to them on the computer. The coordination cost is basically zero. The transaction costs are basically zero.

"For the data on the one survey that I ran, we spent $35 and we had over 2,000 responses from 278 Turkers."

Before using Mechanical Turk for their studies, both Russell and Callison-Burch had to introduce the concept to their respective IRBs, neither of which had dealt with it before.

Callison-Burch says he tapped colleagues at other institutions who had used Mechanical Turk in order to draw up his research proposal. He asked for and received exempt approval after some e-mail exchanges with the IRB.

"They were just asking for more detail," he says. "I believe even one of the board members called me up to ask for a bit of clarification about what Mechanical Turk does."

Russell, who was studying willingness of subjects to disclose personal information online, also applied for exempt status from his IRB.

"It came back, 'Nice try,'" he said with a laugh. "The response was, 'Well, this sounds like people to us and we're not going to let that slide without further investigation.' For the most part, (the proposed study) went through once we conveyed clearly to their satisfaction that we were not holding personal information and we were not doing any manipulation (of subjects)."

Panos Ipeirotis, PhD, an associate professor at the Leonard N. Stern School of Business at New York University in New York City, has studied crowdsourcing and user-generated content on the Internet. In his blog, "A Computer Scientist in a Business School," (http://behind-the-enemy-lines.blogspot.com/) he's looked at the phenomenon of Mechanical Turk and its various uses, including research.

Ipeirotis says the anonymity of the subjects is one great advantage of the system, from the perspective of IRB review.

But he says IRBs have asked questions about how the data is kept secure by Amazon, and about other issues related to the confidentiality and payment of subjects. (see accompanying story).

When to seek IRB review

Callison-Burch suspects that IRBs will begin receiving more proposals from researchers wishing to use it who previously had not dealt with human subjects.

"There are a lot of computer scientists in particular who definitely aren't used to dealing with human subjects," he says. "A large class of computer science research at the moment is data-driven machine learning and for many of our applications we just deal with existing or found data. But I think (Mechanical Turk) really transforms how I as a computer scientist who works with machine learning applications can do things."

One tricky area to navigate will be at what point a task ceases to be human subjects research and becomes something more like engaging outsourced staff.

Callison-Burch acknowledges that the line can be blurry. For his own linguistic work, some professors he consulted questioned whether he needed to apply to the IRB at all. "I did it just to be on the safe side," he says. "You can gather any type of information using Mechanical Turk. It may be that certain studies are much more squarely within the purview of the IRB than others."

Ipeirotis says the rules for research on Mechanical Turk aren't any more complicated than they are for research outside it.

"If you're asking things about codes or the state of the world, asking them to tell you whether something is blue or red, you're not asking them about personal opinions so in that case an IRB is not required," he says. "An IRB is required whenever you are asking people to do an experiment where the outcome depends upon their own personal state."

Russell says that in addition to the survey he conducted on Mechanical Turk, he also gathered responses using more traditional research methods.

One thing that makes Mechanical Turk so enticing to researchers — its protection of anonymity — makes it difficult to know who the Turkers really are. Ipeirotis has done some demographic research of Turkers, posting them on his blog. They tend to be younger, between the ages of 21 and 35. Most are from the United States or India.

Russell says that as we know more about Turkers and whether their responses are generalizable to the greater population, interest in this research method will continue to grow.

"If their reliability comes out to score well (compared to traditional research populations), then there's going to be a lot more people who will consider it legitimate research and a lot more pressure to use it, because it's cheaper and faster." ■

Reviewing research on Mechanical Turk

IRBs must consider anonymity, informed consent

Amazon's Mechanical Turk offers investigators the chance to survey thousands of respondents quickly and cheaply via computer while protecting their anonymity. Once IRBs understand how the system works, approval should be a slam dunk, right?

Not always. **Panos Ipeirotis**, PhD, an associate professor at the Leonard N. Stern School of Business at New York University in New York City, who has studied the use of Mechanical Turk, says IRBs have raised specific questions about its use in research.

Mechanical Turk allows an investigator (or "requester" in the platform's parlance) to post a Human Intelligence Task (HIT) and open it up to thousands of workers ("Turkers") accessing the site from all over the world.

A Turker can choose a HIT, read through it before deciding to perform it, and carry it out, usually in only a few minutes. Once the task has been completed, the requester is able to view it, decide whether it has been fulfilled properly, and authorize a small payment from his or her account to the worker's account. The requester never learns personally identifiable information about the worker.

"I think Amazon's terms of service are really very nicely in line with the type of thing you'd want for an experimental design where you want to keep the subjects anonymous," says **Chris Callison-Burch**, PhD, an associate research professor in the computer science department at Johns Hopkins University in Baltimore, who has used Mechanical Turk for research. "It's pretty much how you would 'anonymize' data from a study that you did in person where you would give each subject a serial number."

Ipeirotis says he's heard of IRBs asking for more detail about precisely how Amazon protects the personal information that it holds — details that Amazon tends to be tight-lipped about providing. In fact, Amazon officials did not respond to a request from IRB Advisor about how the company protects data.

"They're not going to provide explicit information about how they monitor data and who has access," he says. "I just don't think they're going to answer such questions."

Compiling a profile

Ipeirotis says there is another concern about confidentiality that has nothing to do with Amazon's data protection system. Each Turker is issued an individual ID number, which does not change. While a researcher may not know the name of the person assigned to a particular number, if the subject participates in many studies, a fairly detailed personal profile could still be derived from the answers, he says.

"You know from one set of data that Subject No. 123456 is a male and from another experiment what his age is and from another survey you might learn his sexual orientation," he says. "You can ask about zip code, family status, attitude about movies, websites visited. You could build a very comprehensive profile of an individual by using connecting information."

IRBs concerned about this possibility can require investigators to delete the worker's official Amazon ID number and assign them a different ID that is unique to a specific study once the data is collected.

"If people are really concerned about the privacy of their subjects, this should be a standard practice in IRB proposals," Ipeirotis says.

Other issues raised by the use of Mechanical Turk:

—Informed consent — because the entire interaction between the investigator and subject is online and anonymous, it is impossible to obtain a signed consent form. Consent can be obtained in a few ways, Ipeirotis says. If the IRB permits it, a requester can include consent in the request, explicitly stating that the task is research and that acceptance of it constitutes giving consent.

A more in-depth consent statement may be part of a "qualification," which is a test or other screening question used to determine whether the worker is eligible to work on a HIT. That qualification would show up as a separate screen before the worker can participate. He or she could read the consent statement and would have to click a button saying "I consent" before being able to continue to the study itself.

—Payment for unsatisfactory work — Requesters have the option of declining to pay for work completed by a Turker. The reason for

this is to weed out "bad responses" — either by people who simply randomly press buttons or more sophisticated frauds in which people create computer software that makes it appear as though a human is answering.

The latter problem is not a serious concern for researchers, Ipeirotis says, since there's not much money in filling out short research surveys. But it is possible to throw out responses that do not appear to have been done properly and to refuse to pay the Turker. He notes that IRBs usually require that a person be paid regardless of whether he or she withdraws from a study.

One answer to that problem, he says, is a separate qualification that forces participants to answer some questions — unrelated to the research — showing that they're paying attention and to refuse to let them participate in the study if they don't pass the test. ■

23andMe gene test firm uses samples for research

On advice of IRB, revised IC process

23andMe brings a unique twist to the world of commercial genetic testing.

Here, a person can purchase a testing kit, submit a saliva sample, and access a secure online report regarding his or her genotype that links results to research about disease risks, carrier risks, physical traits and drug responses. For an additional fee, the customer also can explore his or her ancestry and even link up with other customers whose DNA closely matches theirs.

But the company also has engaged in research studies, and recently published a paper in the journal *PLoS Genetics*, linking certain genomic variations to physical traits such as hair curl, freckling and a sneeze response to bright light.[1] The information came from customer samples and responses to surveys, both stripped of identifiers.

Editors of the journal initially raised questions about the lack of IRB review. In an accompanying editorial, the editors stated that publication of the article was delayed six months while the issue was resolved. 23andMe obtained an opinion from an independent IRB exempting the study from review, based on the fact that the investigators didn't directly interact with participants or receive identifying information about them.

Finding an IRB

Joanna Mountain, PhD, senior director of research at the Mountain View, CA-based company, said that at first, it was difficult even to figure out how 23andMe would deal with an IRB.

"I had experience with academic institutions, where you knew what IRB you would work with," she says. "I looked around and there was a local IRB in the (San Francisco) Bay Area. We wanted to be able to have some face-to-face discussions about what seemed to be a tricky area of research that many IRBs wouldn't know what to do with."

On the advice of their IRB, 23andMe made some changes to their procedures:

—Previously, they offered customers a single document, containing both the terms of service for the site and informed consent for research.

"If you wanted to sign up for the 23andMe service, you had to commit to the research project," Mountain says. "The IRB advised us to separate those two sets. As it stands now, when our customers sign up, they have to sign the terms of service to get that service but they can then choose whether to be part of research."

Mountain says the vast majority of customers do choose to participate in research — that ability is part of what draws many of them to 23andMe.

—The company now is in the process of contacting people who signed up for the service before the change to get explicit consent to use their data for research.

"Actually, this has been a challenge," she says. "It's set us back a little bit as we wait for people to read the e-mail and do the consent. In some cases, people might not even read the e-mail (immediately). It did cut back a little on our sample size."

—The IRB advised 23andMe to be extremely clear to customers about how the site uses their data and the protections in place. The company already employs animation to discuss such topics as the basics of DNA and how genetic switches control human traits.

"Our IRB is encouraging us to use cartoons and bullet points to explain things," Mountain says. "We haven't implemented it yet. We try to do this all the time — we're so focused on communicating with customers as much as possible."

Outside collaborators

The IRB also is working with the company to review proposals for collaborations with outside investigators that would involve contacting cus-

tomers to be interviewed. Mountain says that any project that goes outside 23andMe's standard information-gathering procedures would require additional IRB review.

She says one challenge of working with customers on a website is getting them to really read the consent forms, since many are used to checking a box for terms of service agreements without reading them carefully. For example, 23andMe highlights the headers of paragraphs so readers can understand the key points.

"We're trying to catch their attention and say, "Hey, this is not like signing up for a newsletter."

She says it's important that her company is able to protect its participant customers without unduly slowing down the process. Mountain says that the impatience of disease communities with the slow pace of research is one factor that has driven interest in sites like 23andMe.

"We've managed to figure out how to work with the IRB to improve on the process," she says. "Rather than have it be a hindrance, the idea is to have it be something that adds value to what we're doing."

For more information about 23andMe, visit the company's website at www.23andme.com.

REFERENCE

1.Ericksson N, Macpherson JM, Tung JY, et al. Web-based, Participant-Driven Studies Yield Novel Genetic Associations for Common Traits. PLoS Genet 2010 Jun 24;6(6):e1000993. ■

Patients work together to amass health data

Aggregate info reported back to members

The CureTogether website allows participants to log in anonymously to answer questions about diseases or conditions they may have and the various treatments they have used, along with the effectiveness of those treatments.

The 2-year-old site, based in Mountain View, CA, aggregates that data for reports published on its website. For example, the company recently ranked the effectiveness of various treatments used by 260 CareTogether participants who suffer from allergies. Written reports are supplemented by easy-to-understand infographics.

Co-Founder **Daniel Reda**, BSc, says the goal was to create an alternative to the traditional health website templates he'd seen on the Web.

"In our experience, you'll typically find a WebMD type of site where there's information provided by experts, or you'll find online communities where patients come together at a condition level to share stories about their experiences," Reda says.

He says typical online health communities provide a lot of anecdotal information, but little in the way of numbers.

"We wanted a site where you could find out how many people said they'd tried a given treatment, and what percentage of them had a positive experience," Reda says.

International reach

The site started with three conditions, all in the area of women's health, and has grown to include information about more than 600 different conditions, Reda says. More than 15,000 members in 112 countries have contributed more than 1.4 million data points (snippets of information gleaned in surveys).

Reda says organizers of the site consulted ethicists when they first began, who urged transparency about how the data would be used and minimizing the collection of personally identifiable information.

"A key part was deciding not to show individual member data, to only show aggregate information," Reda says. "Our site has been from the beginning about sensitive conditions — we started off with women's health conditions that many women sometimes don't even feel comfortable talking to their doctors about."

A person signs up by providing an e-mail address, which doesn't go any further than CureTogether's database, Reda says. The company sends e-mails about updates on any conditions the person specifies, and participants have the ability to opt out of that use.

CureTogether has worked with pharmaceutical companies and individual investigators to send IRB-approved recruitment messages to members, but doesn't release their e-mail addresses. Beyond the e-mail address, the company collects almost no demographic information. Patients can opt to submit their gender, country and Zip code.

"There is no way to view an individual member's information," Reda says. "We are always mindful of protecting patient privacy."

Self experiments

When an outside investigator collaborates with CureTogether, the project is reviewed by the researcher's IRB and all messages distributed must contain IRB-approved language. While Reda expects those collaborations to continue, he also sees potential for growth in the field of self-experimentation.

Currently, members can use tools to help track their symptoms over time. Eventually, Reda says, the company wants to help people set up their own experiments to test the effectiveness of interventions.

"For example, a patient might suspect that a certain vitamin might be having a certain affect on (his or her) headaches," he says. "We would help do the experiment properly, in terms of having a baseline of a few days of not trying the vitamin, and then (once the person starts taking it) we could help chart any symptoms.

"We can provide them with the tools where we can do the complex math that would give them a sense of how statistically significant something is," Reda says. "So that they would know whether it's a real effect or whether it could be just explained by chance."

He says there is potential for expanding this service to allow different people who want to undertake similar experiments to work together, even offering to randomize to different treatments by computer if they wish.

Reda acknowledges that this starts to raise questions about safety and risk that traditionally have been overseen by IRBs. He says CureTogether is part of a group known as The Quantified Self (QS), which gathers people interested in self-data collection and experimentation.

In a recent post on the QS blog, Reda raised the question of how to handle ethical review of self-experiments that invite others to join. He argued that the QS community should either assemble its own ethical review board or figure out a way to help like-minded people pursue their experiments without "advertising" studies in ways that too closely resemble research recruitment.

"It would be truly tragic if the nascent QS movement, and its promise for social benefit, became overburdened with regulatory oversight for failure of its pioneers to take appropriate safety precautions," Reda wrote.

For more information about CureTogether, visit the company's website at www.curetogether.com. ■

CNE/CME OBJECTIVES

The CNE/CME objectives for IRB Advisor are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

■ Privacy issues are priority in some international research

■ Check out these protocol review best practices

■ Facebook studies raise unique issues

■ New data on incidental findings has implications for IRBs

■ What to include in consent for Phase I studies

CNE/CME QUESTIONS

21. Top U.S. officials recently apologized to the Guatemalan people after disclosure that they were subjected to an unethical experiment by the U.S. Public Health Service in the 1940s. What did the experiment involve?
A. Families were exposed to unsafe levels of radiation
B. Hundreds of people were intentionally infected with syphilis
C. Children were forced to take the polio vaccine despite parental concerns about its safety
D. Guatemalan soldiers were infected with malaria and not offered treatment

22. Why should IRBs consider viewing research into virtual worlds like the online site called Second Life as human subjects research?
A. The people behind the online avatars have real feelings that could be affected
B. Researchers who deliberately provoke an online avatar might cause emotional pain
C. The screen names could be traced back to the actual people
D. All of the above

23. Personally identifiable information about people completing surveys on Amazon's Mechanical Turk:
A. is held by Amazon.
B. is held by researchers.
C. is never collected.
D. None of the above

24. The genetic testing company 23andMe was advised by its IRB that informed consent for research be separated within the company's terms of service agreement
A. True
B. False

Answers: 21. B; 22. D; 23. A; 24. A

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