IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

INSIDE

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Bypassing an IRB Review, Researchers Held Herpes Vaccine Trial on an Island

Is this start of new trend?

By Melinda Young, Author

The human research protection community recently learned of a troubling clinical trial that involved private funding, a U.S. medical college researcher who died this summer, and a study held on a Caribbean island.

The troubling part is that the clinical trial was for a live attenuated herpes simplex virus-2 (HSV-2) vaccine injected in human participants, and it was never reviewed by an IRB.

"I have to admit, this is very shocking," says **Brenda Curtis**, PhD, MSPH, an IRB member and researcher, as well as an assistant professor in the department of psychiatry at Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

> THE CLINICAL TRIAL WAS FOR A LIVE ATTENUATED HERPES SIMPLEX VIRUS-2 (HSV-2) VACCINE INJECTED IN HUMAN PARTICIPANTS, AND IT WAS NEVER REVIEWED BY AN IRB.

It's standard practice for university-affiliated researchers to obtain IRB approval — even for research that is privately funded. Researchers can go through their own institution's IRB review process, or seek an IRB's approval in the nation where the research is being conducted.

Neither happened in the case of the herpes vaccine trial, which was conducted by Rational Vaccines of Springfield, IL, and **William Halford**, PhD, a professor at Southern Illinois University (SIU)

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School of Medicine in Springfield. Halford and **Agustin Fernandez** III co-founded Rational Vaccines in 2015. Halford conducted the herpes clinical trial in 2016, and died in June 2017 from a rare cancer.

Halford brought study participants to the island of St. Kitts, where they were injected with the investigational vaccine. It's unclear whether the participants gave informed consent. Rational Vaccines did not respond to repeated requests for an interview, but Fernandez has written about the vaccine trial on his Facebook page, saying that it is about patients being able to take healthcare into their own hands and doctors having more control than lawyers.

In a Foundation for Economic Education article link on Fernandez's Facebook page, there is a reprinted blog entry by Halford that expressed Halford's frustration with the FDA and federal research bureaucracy. The blog entry of July 24, 2016, reads, "…The fact that 1 million people worldwide will, this week, contract new HSV-1 or HSV-2 infections has no bearing on their standing within the machine that is the FDA … We can bitch, we can moan, or we can just say, 'Let's go to the other 95 percent of the world not under the FDA's thumb and get a functional HSV vaccine out there and start helping people.'" *(The article is available at: http://bit.ly/2xBXgBW.)*

The idea that IRBs are major factors in research delay is not accurate, Curtis says.

"I've seen very detailed human subjects protocols go through the IRB in a fast-paced time because they were well-written and well-thought-out," she says.

Protecting human lives is worth waiting an extra month or two, Curtis adds.

One study participant, Rich Mancuso, went public with his experience in the trial, saying he was recruited on Facebook and believed the vaccine stopped his severe outbreaks. On his Facebook page on April 24, 2017, Mancuso called his involvement with Rational Vaccines' HSV-2 vaccine a "happy ending."

This herpes vaccine case is part of a recent trend and cultural shift away from the four-decade-long focus on research participant safety, which some people believe has resulted in a loss of lives as individuals wait for new treatments and cures.

"We're seeing a huge push from the participant rights base, and we're seeing it through different channels," says **Elizabeth A. Buchanan**, PhD, endowed chair in ethics and acting director of the office of research and sponsored programs at the University of Wisconsin-Stout in Menomonie.

Going forward, this cultural shift will involve questions about expertise and who makes decisions and who is in control of research, Buchanan says. "There's a pushback to the FDA."

Some people take the stand that they will not work in the system because what they're doing is for the betterment of society, she says.

"I think it's risky," Buchanan says. "There is a reason there are safeguards in place, and IRBs are flexible enough, and the FDA does a very good job of approving experimental treatments."

The bigger philosophical and ethical issue is that this is part of a shift away from the idea of an expert.

"Zero in on the social media piece," Buchanan says.

"People recruit on Facebook, which is a very different vibe than traditional recruiting and advertising for a clinical trial," she explains. "This is making use of all these new outlets, while capitalizing on the idea that we're in a time of questioning

authority and moving away from any acknowledgement of expertise or authority or know-how or experience."

Some people are pushing back against the things that lead to good science, she adds.

Rational Vaccines' vaccine trial results have not yet been published in a peer-reviewed journal, and there are some potential consequences of the company circumventing research regulations. For instance, the Ministry of Health in St. Kitts issued a news release, stating the two-island nation had not been approached about the vaccine project. The nation's chief medical officer also said the nation plans to investigate the clinical trial. *(The statement can be found at: http://bit.ly/2yaSXgs.)*

When asked if SIU's IRB, the Springfield Committee for Research Involving Human Subjects, had exempted the study from IRB review, an SIU spokesperson replied that the IRB did not make a decision on exemption because the issue was never brought to the IRB for review.

"To be clear, the IRB and the university are reviewing whether the research and any trial should have been brought to the IRB by the primary investigator, since his research was conducted by a private company, Rational Vaccines — not SIU," says **Karen Carlson**, director in the office of public relations SIU School of Medicine. Carlson also says that the university is reviewing its procedures and communication with principal investigators concerning any research they perform independently from their roles as faculty members.

The medical university IRB's policies state that it is responsible for reviewing proposed research that includes humans as subjects when the study is conducted by a member of the research institution's faculty, staff, residents, and students.

This is a policy that many academic researchers would understand. "I have always assumed that any research I carry out, once I was a student, employee, or faculty — any research I conduct or participate in — has to be IRB-approved, even if I'm doing contract work," Curtis says.

"I still went through my IRB, even if it's for them to tell me I need IRB approval from some other place," she adds. "I always assumed that's the way to go."

THE FDA IS UNLIKELY TO APPROVE THE VACCINE UNTIL IT HAS GONE THROUGH FURTHER RIGOROUS AND IRB-APPROVED CLINICAL TRIALS.

Curtis works with corporations in research projects, and they often seek review from external IRBs rather than using the local IRB.

"You send protocols to the IRB, and there's no reason to not have it done," she says. "It's not like you couldn't have gotten someone to approve your protocol."

The Theravax HSV-2 vaccine study enrolled 20 American participants, who flew to the Federation of Saint Kitts and Nevis multiple times to receive the vaccine. Halford spent 15 years on herpes immunology research, including studies showing the safety of using a live-attenuated virus vaccine, according to "Game Changer," an article published by the SIU.

Rational Vaccines reported that the participants were already infected with herpes. They volunteered for the study in hopes it would mitigate outbreaks of the virus and alleviate symptoms. Rational Vaccines also reported that there were no adverse effects during the trial and that the vaccine was a success.

However, there are no regulatory agencies reviewing the study's outcomes, so it's difficult to independently verify the company's claims. The FDA is unlikely to approve the vaccine until it has gone through further rigorous and IRB-approved clinical trials. When asked about whether Halford had provided any information about informed consent, vulnerable populations, and adverse events to the SIU IRB after the clinical trial was completed, SIU's Carlson answered, "No."

"Dr. Halford did not bring any information to the IRB because this was not an SIU study," she says.

SIU SOM issued a statement in late August, acknowledging that Rational Vaccines licensed intellectual property from SIU through SIU's office of technology transfer. Within that license agreement, both Rational Vaccines and SIU are responsible for upholding all applicable laws and regulations associated with the license.

The statement also says that SIU is not responsible for trials and research conducted by independent companies.

"I haven't had any communication with [Rational Vaccines]," Carlson says. ■

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IRB Collaborations With Tech Companies Could Mean What to the IRB?

2014 Facebook study invites caution

Tech companies increasingly are partnering with research institutions. These partnerships include sharing data and project collaboration. What IRBs will want to know as this trend continues is what it means from a human research protection perspective.

"We're seeing these ongoing and growing connections between academic researchers and industry," says **Elizabeth A. Buchanan**, PhD, endowed chair in ethics and acting director of the office of research and sponsored programs at the University of Wisconsin-Stout in Menomonie.

"What's happening is, more and more, research is sponsored by industry or a collaborative with industry," Buchanan says. "We're seeing these challenges, and we want to talk about these ethical and practical challenges that arise."

Researchers can learn a great deal from social media data, says **Brenda Curtis**, PhD, MSPH, an IRB member and researcher, as well as an assistant professor in the department of psychiatry at Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

Curtis has worked with Facebook and app developers on studies of populations of people who are seeking treatment for substance use disorder.

"I use language analysis to predict relapse," Curtis says. "We're using the social media language of people who consented to our study. There's an opportunity for researchers to work with tech companies and big data companies like Facebook in order to help improve health," Curtis says.

"More researchers are seeing the benefits of big data and they access data sets," Buchanan says. "It's changing how we do research, fundamentally, and IRBs need to know what to ask and how to think through a purchased data set."

From a social-behavioral research perspective, researchers and tech companies share a curiosity and interest in learning more from social media data, including Facebook and Twitter.

The IRB's role is to ask questions about the data set, including asking where it originated, Buchanan says.

Using tech companies' big data can lead to important research. Buchanan has seen how social media data can better inform research into illegal drug use in urban areas. But it's important for all investigators to outline to the IRB how they'll protect data subjects' privacy and safety.

"IRBs want to make sure we don't have another Facebook emotional contagion problem," she says. "So, we should review those projects."

In 2014, Facebook and Cornell University of Ithaca, NY, were criticized for conducting a study not reviewed by an IRB. Called "Experimental Evidence of Massive-scale Emotional Contagion through Social Networks," the study was published online June 2, 2014, in *Proceedings of the National Academy of Sciences*.

Cornell issued a statement at that time about how the research was conducted independently by Facebook and a Cornell professor only had access to results, which was why the Cornell University IRB concluded it was not subject to review. *(The Cornell University statement can be found at: http://bit.ly/2hAAMuN.)*

Facebook had changed its content on news feeds for users, chosen randomly. It adjusted the balance of positive and negative posts, with one group seeing mostly positive posts and another seeing mostly negative. The study looked at whether the emotional content of news feeds affected the emotional content of users' own status updates. It found that it did affect news feeds, reflecting what users saw. No informed consent was obtained. *(See story about the Facebook study in the December 2014 issue of* IRB Advisor*.)*

"What have we learned, and has Facebook changed any internal policies since that experience?" Buchanan asks. "I don't know the answer yet. Collectively, we've moved so quickly into accepting large data, big data sets, and accepting where they come from, whether Twitter or an aggregator site."

The study had involved manipulation of multiple things — not just the negative versus positive words — and the effect was small, Curtis says. But the case did create caution among tech companies, researchers, and IRBs, she notes.

"Researchers will be more cautious in how we explain studies when we work with big data and are doing testing," she explains. "Facebook has set up some internal review boards and policies, and published a couple of articles on it."

Research institutions and tech companies can have a variety of arrangements. These include an institutional researcher partnering with the tech company or contracting for access to certain data, Buchanan says.

Tech companies might seek this collaboration to add academic integrity to the research and to reach a broader audience, she says.

IRBs can ask the following questions:

- How were these data collected originally, and for what purpose?
- How is the information now being used?
- Are there provisions in place that prohibit people from attempting to reidentify data, including provisions in data use management and agreements?
- What are the origins of the data, and how you are using them?
- Are there secondary or tertiary privacy concerns that come with reuse of data?

"We've moved away from a basic understanding of privacy into a complex place as data are used [in] more and more contexts, providing more opportunities for privacy to be challenged," Buchanan says.

One way for an IRB to stay on top of these changes is to provide educational sessions on the institution's rules regarding the use of social media data or collaborating with a tech company, Buchanan suggests.

"Make sure researchers, and maybe IRBs, too, are familiar with a particular social media platform," she adds.

If they learn about Facebook, Twitter, Instagram, etc., they might come up with better ethical questions to ask before jumping into a research collaboration.

"And we've had interesting questions about the providence of data," she adds. "For instance, if a data set is breached and a researcher has access to it, is it okay to use breached data, like data from WikiLeaks? And lots and lots of researchers are using those data."

When data are from a dubious source or an unethical source, what does that mean for the scientific enterprise that plans to use the information?

Those types of questions drill down to the fundamental integrity of research and are more for an ethicist or philosopher to ponder than for an IRB to ask, she adds. "Just because data exist, are they there to be studied?" she asks. ■

The Choice: A Decision to Decline a Clinical Trial

IRB member and bioethicist found decision difficult

Ten years ago, **Rebecca Dresser**, MS, JD, faced a life-changing and, quite possibly, life-saving decision. As a bioethicist and IRB member, she was informed of a diagnosis of cancer and offered a difficult choice: She could enter a new clinical trial for treatment, or follow a specific regimen recommended by oncologists on a tumor board.

As Dresser describes it in her new book *Silent Partners: Human Subjects and Research Ethics*, the board recommended a regimen that included a new chemo drug that had just been approved for her type of cancer. Considering also that qualifying for the trial might delay treatment, a "terrified" Dresser reluctantly turned down the opportunity to be a research subject.

She had mixed feelings about it, knowing that other research subjects had participated in trials to prove the effectiveness of the new drug she would now be taking. The treatment worked and she survived, but this existential moment of weighing clinical trial participation versus personalized treatment spurred an interest and empathy for research subjects faced with similar decisions. The result was her book. *IRB Advisor* recently interviewed Dresser, a law professor at Washington University in St. Louis, and the questions and answers are summarized as follows.

IRB Advisor: You made a choice as an IRB member who was a potential research subject. What were some of the factors that went into your decision?

Dresser: I had the opportunity to be in a treatment trial, but I was also offered a regimen the tumor board recommended. It included a new chemo drug that had just been approved for my kind of cancer. That was in the regimen the tumor board recommended for me. I didn't like the idea that I wouldn't have at least a chance to get that [drug] in the trials and I asked whether that would delay my treatment if I went to the trial. If you go into a trial, you have to be screened and half the time you don't even qualify. Even if you do,

you have to be randomized [into one of the research arms]. I was really in a lot of pain and discomfort and I wanted to go into treatment. The idea that it would delay my treatment wasn't very appealing, so those were the main two reasons I said no. Even though I realized I might be wrong. It might turn out that the trial was just as effective and maybe with fewer side effects, but I just felt that here was this recommendation a bunch of experts had come up with for me as an individual.

IRB Advisor: How did this experience inspire your book, *Silent Partners*?

Dresser: It got me interested in what other subjects think about their research experiences. I started reading a lot of literature, everything from journalist interviews with subjects and sometimes research subjects writing about their own experiences. There are a lot of empirical studies of what subjects think, so I read a lot of that. I also read fiction that was written from the subject's point of view, and that's how I put the book together.

IRB Advisor: IRBs sometimes have a member of the community on a board, but is it uncommon for IRBs to include someone who has been a subject in a clinical trial?

Dresser: It happens, and other people on an IRB might have been in clinical studies, but there is no intentional effort to do that. I recommend in the book appointing more research-experienced subjects to IRBs, even just to add it to the potential qualifications for somebody. Has the researcher ever been a subject? That's a bonus point. There is an issue of having one or two people [with this background], but you have to worry about representativeness. You don't want to get people who had a totally wonderful or a totally awful experience and nothing in between.

And even then, what happened to a research subject is not necessarily what happens to all subjects, but it is better than nothing. I know one IRB that has something called "volunteers for health," which is a bunch of people who have been in studies and they are willing to think about other studies. If you can find some people who have been in different types of studies, you could have an advisory board. Then, if an IRB gets a cancer study or something that is raising a lot of issues, they can ask for advice from people who have been in similar studies. In the education that IRBs often offer the research community, they can have some sessions where they bring in some past research subjects and have them talk about what happened to them and offer their views on things.

"EVEN SOMEONE WHO IS VERY FAMILIAR WITH RESEARCH MAY NOT GET A SENSE FROM THE CONSENT PROCESS THAT AN ADVERSE OUTCOME IS A REAL POSSIBILITY."

IRB Advisor: Has this been a kind of blind spot in the research review process?

Dresser: In my reading, I found various remarks suggesting that this would be a good idea, but nobody really has picked up on it and run with it. In the book, I discuss the tradition of self-experimentation, where researchers used to try things on themselves first. Part of the reason they did that was that it was a way to educate themselves and it helped them design their regular studies. This still goes on to some extent, so I advocate that we would bring that back — not that you are experimenting on yourself, but that you are volunteering for other studies people are doing as a way to educate yourself about the things that might matter to subjects. Usually, if you are working at a research institution there are all sorts of trials going on. Finding out more about what subjects think could be helpful in recruitment of [future] subjects. I think it has a kind of professional research aspect to it.

IRB Advisor: What kind of perspectives do research subjects bring to the discussion?

Dresser: In my research, one of the things I've found was that subjects really care about how they are treated. You might think of it as trivial, but are they treated with courtesy? Are their appointments on time? Do they have to wait around, and what's the waiting room like? Is the staff rude, condescending, or disorganized?

They see all of that as part of respect for the research subjects. I don't know if that is something IRBs would be directly involved in, but certainly it would be something to talk about in the education of researchers. I really think for most subjects, their study appointments are an inconvenience. You have to take time off from work, get a babysitter, and take time out of your day, so the minimum number of study visits necessary to get the data is a real consideration. If you have more than necessary, that is really a burden on subjects, and they talk about that.

IRB Advisor: You mention that

you sent in a comment when the Common Rule was being finalized, but there is no requirement to include subjects in the manner you describe.

Dresser: It doesn't necessarily have to be in regulations. The person who is an unaffiliated member of the IRB [could be a research subject]. IRBs could easily start thinking about this on their own. There is nothing in the regulations that suggest this would be inappropriate. When I talk to people about this issue, even people who are on IRBs or are researchers, I usually get a few comments from the audience from people who have been subjects. They thought they got some benefits from that [that they could share]. Things like the disclosure and consent process. One woman said the informed consent warned of possible flu-like symptoms. She said, "that's not going to happen to me," but it did and she had to take time off work that she was not prepared to take. Even someone who is very familiar with research may not get a sense from the consent process that an adverse outcome is a real possibility. There are ways to make consent language [more clear] and more meaningful and also learn about potential burdens and benefits of study participation that researchers may not be tuned in to. ■

IRBs Could Address Ethical Issues Related to Tracking Devices

Mobile devices raise new concerns

Some IRBs have begun to review studies that use medical devices with tracking technology. These types of mobile devices raise some ethical and regulatory questions.

"The bigger question is whether the regulatory agencies will provide further guidance on the use of these features in medical devices and how their use will fit into current regulations," says **Linda Reuter**, MS, CIP, director of Biomedical Research Alliance of New York (BRANY) IRB in Lake Success, NY.

Reuter was among those involved in CITI committees that reviewed the use of such devices and their data security, data management, access, and monitoring.

"We were asked to go and represent the IRB perspective as a small piece of a larger question about the research use of mobile technology," Reuter says.

Mobile devices include any wearable medical technology, including EKG monitors, accelerometers like Fitbits, and glucometers. They collect real-time data about patients, and the information can be seen by clinicians and researchers.

Another issue that makes reviewing this new technology challenging for IRBs is that traditional clinical trials usually do not provide real-time data. Under the traditional model, the research participant will come in for visits in a controlled environment. Mobile device technology involves transmitting data in new ways and possibly giving participants access to data without the benefit of having someone there to help them interpret what it means.

"The role of the IRB is to protect the rights and welfare of subjects, so we're not concerned so much with the technical aspects of the device, as we are concerned with whether they pose any risk to the participants in the study, and exactly how they will be impacted," Reuter says.

Also, there's the question of data integrity and whether participants are even wearing the device as expected.

The following are some of the questions an IRB might ask about these devices in a trial:

- Is there any risk to the subject, physical or psychological, in wearing the device?
- How do investigators know whether the research participant is wearing the device and not someone else?
- Are there any benefits to wearing the device?
- If the device produces specific information, is it visible to the subject?
- Could the subject ask for information about what the data mean, or not?
- What will be done with any incidental findings?
- Are data transmitted by the device secure, private, and safe?
- What are subjects being told about how the information will be used?
- What do subjects need to do for their own safety when wearing the device?
- If a subject's mobile device alarm

sounds, indicating a potential health crisis, where is this reported?

• How does wearing this device affect the participant's safety and welfare?

• Does the informed consent document properly inform research participants of these issues?

The BRANY IRB is working on making sure its informed consent language is clear about what type of data are collected with the device, how the data are used, and which data are available to subjects. The IRB also wants the informed consent to be clear about how subjects should report any information that's collected and what should be done with that information, Reuter notes.

"We have seen one study for epilepsy or a seizure disorder where they used a portable device to detect changes in physiological measures to predict when the seizure would occur," she says. "That study was establishing a baseline."

Most of the IRB's questions were related to what sort of information would be given to subjects in the consent form. There were no clinical decisions made in the study, as it was a feasibility study to see if standard data matched data from the portable device, Reuter explains.

"As guidance comes out on how manufacturers can frame their studies, more device manufacturers will want to do studies and get their technology approved," she says. "If they submit to the FDA for approval, they'll want to make sure the data is valid and will support an application for approval. Therefore, it is very important that the study designs are valid."

The IRB is concerned with the subject's rights and welfare in wearing the device and handling data.

"We're concerned with how to handle safety signals and, also, whether a particular device can pick up incidental findings," Reuter says.

"In traditional studies, there have been situations where we discover information we were not necessarily looking for, such as picking up a tumor on an MRI when this was not the intent of the study," she continues. "Mobile technology may also present us with incidental findings. We need to plan ahead for what we will do with that information if it is discovered."

Another data integrity issue involves what happens to the real-time data as they are securely transmitted.

"Biostatisticians are weighing in on how this data needs to be transmitted and transformed," Reuter says. "We need to make sure it's not altered while being transmitted securely."

There also is the possibility of research participants being lulled into believing their health is fine since the mobile device is collecting real-time data and they haven't heard from their physician.

"It's a false sense of security," Reuter says. "They might be lightheaded and not call the doctor because they're wearing the device and feel like someone would call them if something was wrong."

Federal regulations must catch up with these kinds of technological changes, she says. The FDA hasn't made any major changes to their regulations in several years, but will issue guidance to reflect changes and help IRBs apply the regulations to emerging research issues. In the case of mobile technology, there was a very helpful guidance document about mobile medical applications issued in February 2015, Reuter says.

"Additional guidance will be needed as this technology moves forward," she adds. ■

HHS to Take Action to Protect Research Whistleblowers

Government watchdog report reveals fear of reprisals

The Department of Health and Human Services (HHS) is taking measures to protect whistleblowers who express concern about human research trials, agreeing with a government watchdog report that the current system has a chilling effect due to "fear of reprisal."[1]

"We concur with the recommendations in the report," **Don Wright**, MD, MPH, acting assistant secretary of HHS, wrote in a letter to the Office of Inspector General (OIG).

The HHS Office for Human Research Protections (OHRP) "will inform complainants of how they can potentially obtain whistleblower protections by concurrently reporting their allegations of noncompliance with human subject research protections to entities such as OIG or the HHS-awarding agency," Wright wrote in the letter.

"This information will be posted on OHRP's website for complainants to potentially obtain whistleblower protections."

OIG reported that complainants about human research may include the subjects in the trial, employees of a research facility, and other advocates for safe and ethical trials.

"Employees of research institutions (e.g., researchers or study coordinators) with insider knowledge of the circumstances can help identify noncompliance in human subjects research earlier than other complainants or OHRP oversight activities," OIG reported. "Such information allows OHRP to address any noncompliance, hold institutions accountable, minimize risk to human subject volunteers, and ensure public confidence in federally funded research. However, when employees are considering whether to disclose information about potential noncompliance, they may fear reprisal, such as demotion, suspension, or termination. For such complainants, information regarding whistleblower protections may encourage disclosures of noncompliance."

Examples Cited

While the report did not give specific examples, an OIG representative provided *IRB Advisor* with descriptions of some of the incidents reviewed in making the recommendations, summarized as follows:

• A complainant provides several examples of noncompliance, particularly with cancer research trials. The allegations include the research is not reviewed by the IRB, researchers are not following IRB procedures/paperwork submissions, and the IRB has no protocols for the reporting of adverse events.

• Complainant on a medical center nursing staff that assists with neurosurgeries alleges that when patients sign up for a particular research study, the surgeon delays surgery a few weeks in order to obtain the appropriate research equipment for the surgery. The nurse believes this is not in the best interest of the patients. Other nurses have voiced concerns, but were reassigned.

ACCORDING TO OIG, THE COMPLAINANT MUST BELIEVE THERE IS EVIDENCE OF A "SUBSTANTIAL AND SPECIFIC DANGER" TO HEALTH AND SAFETY, OR A VIOLATION OF LAW OR REGULATION DESCRIBED IN THE HHS CONTRACT.

• A resident in the ophthalmology service of a large hospital alleges children and adults are enrolled in research that is not IRB-approved. Research involves injection of chemotherapy to treat retinoblastomas and there have been adverse events. Many research participants do not speak English, informed consent is inadequate, and consent forms are not provided in the participant's native language. Complainant is not comfortable complaining and does not want retaliation.

• Complainant is a student-athlete with a university scholarship and needs to be cautious because allegations could affect his situation and career. He alleges that students do not have a choice about whether to participate in athletic testing research. The coach is in the room during the informed consent process and the student alleges that the research has blanket IRB approval, meaning that additional testing can be included without additional consent. The researchers are coaches as well as teachers, so students feel that refusing to participate may result in poor grades and/or a loss of their scholarships.

Step Up Protections

While those seem to be valid concerns, the problem arises in reporting the incidents in a protected manner that would ease fears of retribution.

"Under certain circumstances, employees at research institutions with HHS-funded grants or contracts may be entitled to relief commonly called 'whistleblower protections,'" the OIG report states. "Such protections may be available if an HHS contractor, subcontractor, grantee, or subgrantee takes a prohibited employment action (e.g., termination) against an employee for making a 'protected disclosure.'"

For the employee's disclosure to be considered protected, according to OIG, the complainant must believe there is evidence of a "substantial and specific danger" to health and safety, or a violation of law or regulation described in the HHS contract. However, a "disclosure to officials

of a regulatory oversight agency such as OHRP does not qualify as a 'protected disclosure' for the purposes of whistleblower protections."

Nevertheless, whistleblower protections may be available if complainants disclose such noncompliance to other entities, such as OIG or the HHS grant-awarding agency.

"Providing information about these available whistleblower protections could encourage complainants to come forward and thus help OHRP identify actual or potential problems," OIG recommended. "OHRP should post this information prominently on its website and include it in routine outreach to research institutions."

In addition, OIG offered to provide assistance to OHRP via its Whistleblower Protection Ombudsman on how potential complainants can make a protected disclosure.

"OHRP should coordinate with the HHS grant-awarding agencies to ensure that they relay to OHRP any allegations they receive," OIG recommended.

Wright wrote in the letter that these actions will be taken. "We will notify HHS grant-awarding agencies of this process and request that they relay to OHRP any allegations of noncompliance with HHS regulations at 45 CFR Part 46," Wright stated. "[W]e will ask HHS leadership to consider the adequacy of the proposed whistleblower protections for complainants in making disclosures about human subject protection to OHRP. We agree that elevating this issue could help HHS determine whether it should seek a legislative change that enables the OHRP and other HHS entities that are not responsible for contract and oversight management to receive protected disclosures." ■

REFERENCE

1. Office of Health and Human Services. Office of Inspector General. OHRP Should Inform Potential Complainants of How They Can Seek Whistleblower Protections. OEI-01-15-00351. September 2017. Available at: http://bit.ly/2wYkRs5. Accessed Oct. 10, 2017.

Brain Reanimation Investigator Reports Dramatic Results

Findings have yet to be published in a peer-reviewed journal

Though the findings come with a considerable caveat — they have yet to be published in a peer-reviewed journal — the lead investigator of a controversial brain reanimation study using "living cadavers" is reporting some dramatic results.

Himanshu Bansal, MD, who is conducting the research at Anupam Hospital in Rudrapur, India, for Revita Life Sciences, described some preliminary results in an email interview with *IRB Advisor*. This was after a press release cited very encouraging initial findings, including minor observations on blood pressure changes, response to painful stimuli, eye opening, and finger movements.

"These reflexes clearly demonstrate that the person is not brain dead," Bansal said in the email. "We confirmed it by EEG, which showed improved electrical activity. One of the patients even came off of a ventilator. We feel the patients will first land in a persistent vegetative state, and from there we will attempt to bring them to a useful conscious state. We are sharing soon our early results through peer-reviewed publication."

Though it is approved only for research in India, the study is registered on ClinicalTrials.gov as a "Nonrandomized, Open-labeled, Interventional, Single Group, Proof of Concept Study With Multimodality Approach in Cases of Brain Death Due to Traumatic Brain Injury Having Diffuse Axonal Injury." No results were reported on the site as this story was filed and it lists the estimated study completion date as July 2018. Bioquark Inc. in Philadelphia still is listed as one of the sponsors, and an official there confirmed the trial is ongoing after it ran into a regulatory snafu in India.

"Revita is running things in India, but Bioquark is still a part of the project," said **Ira S. Pastor**, BS, MBA, Bioquark CEO. "There was a bit of a local battle that put things on hold for several months. The study was inappropriately removed from the Indian Council of Medical Research (ICMR) database. However, the ICMR has no regulatory oversight on such research in India, and the group that actually does, the Central Drugs Standard Control

Organization (CDSCO), Drug Controller General of India, had no objection to the program progressing, and finally issued a letter to Revita regarding this."

Thus the study continues, with Bansal subjecting the research subjects to interventions that include stem cells, biologics, laser therapy, and nerve stimulation. *(For more information on the study, see the story in the July 2016 issue of* IRB Advisor*.)*

"We can't say as of now if the changes are due to stem cells, median nerve stimulation, or laser, or if it is just because of prolonged observation and natural recovery rate," Bansal said.

Subjects between the ages of 15 and 65 that have been declared brain dead from a traumatic brain injury are being recruited from area hospitals. The living cadavers must not be indicated for organ donation, have no cranial implants, and cannot be pregnant. As approved by the IRB in India, informed consent must come from family members of the research subject.

The study was originally questioned for delving into the gray area between life and death, but the main ethical and legal constraint is that one cannot work with living cadavers in research that involves harvesting organs, Pastor said.

Bansal still holds out hope that the study will lead to some breakthrough in regenerative therapeutics, while raising profound questions about the line between biological life and death.

"This research will open the door to review the concept of irreversibility of cell death," he said. "When should we declare irreversible cell death? Up until what time frame can it be reversed? It will definitely help in treating patients with comas and other neurological diseases." ■

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CME/CE QUESTIONS

1. **According to IRB experts, what is the most controversial issue related to a recent clinical trial for a live attenuated herpes simplex virus-2 (HSV-2) vaccine injected in human participants?**

   a. It had greater than predicted adverse events.
   b. The study failed to show positive results.
   c. The study was never reviewed by an IRB.
   d. The study's funders were arrested.

2. **When researchers collaborate with tech companies, collecting and analyzing big data, what are some questions IRBs might ask of the study?**

   a. How were these data collected originally, and for what purpose?
   b. Are there provisions in place that prohibit people from attempting to reidentify data, including provisions in data use management and agreements?
   c. Are there secondary or tertiary privacy concerns that come with reuse of data?
   d. All of the above

3. **While advocating education and empathy with research subjects, Rebecca Dresser, MS, JD, said that IRB members who volunteer for studies risk losing a necessary objective view of subsequent research proposals.**

   a. True
   b. False

4. **The "living cadavers" in a study of brain death in India must not:**

   a. be indicated for organ donation.
   b. have cranial implants.
   c. be pregnant.
   d. All of the above

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