IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

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Protecting illegal immigrants in behavioral, clinical research

IRBs should be sensitive to groups' unique vulnerabilities

As the national debate about illegal immigration heats up across the country, researchers continue to work to include such immigrants in their studies.

It can be a difficult task convincing immigrants to overcome their fears of deportation and assuring protection of the data collected from them.

But researchers say it's important to study the health of this large and important group. The Pew Hispanic Center, a non-partisan research organization based in Washington, DC, estimated last year that there were 11.5 million to 12 million undocumented immigrants in this country, about half of them from Mexico.

"I think it is a very sensitive issue, but I think it's an issue that this country needs to have a conversation about and be informed about," says **E. Richard Brown**, PhD, director of the Center for Health Policy Research at the University of California, Los Angeles. "And the best way to have an informed conversation is for there to be good research conducted with and about this population."

Even clinical research, which brings more risk to a vulnerable population, can and should be ethically conducted with this group, says **Ken Goodman**, PhD, director of the Bioethics Program at the University of Miami in Miami, FL.

"Clinical research is ultimately done for the sake of the people who are going to show up in clinics," Goodman says.

"The whole engine is so driven by profits and careers that we sometimes forget that we do the research for the sake of the populations we have the privilege of serving," he says. "If you're in California, Texas, Florida, Illinois, or New York, that's going to include a fair number of undocumented immigrants. And to say we're going to exclude them because we can't get our act together is, I think, to surrender."

Medical research involving the undocumented population benefits the public as a whole, says **Marc L. Berk**, PhD, senior vice president for health policy and evaluation at the National Opinion Research Center at the University of Chicago, Chicago IL.

"Even a policy maker who's very anti-immigrant can still understand the argument that no matter how you feel about immigrants, it's really not good to have thousands of people running around with infectious diseases," he says. "Despite all the problems, it's a population that needs to be studied. There's a lot of noise out there, but not enough good research."

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Berk and others believe that the recent public debate regarding immigration policies already has affected the willingness of illegal immigrants to participate in research, just as it has made them more reluctant to seek out health care.

"We know the debate is affecting participation in [health care] programs," he says. "I'm positive that it would affect survey participation, which after all is not as important as getting health care."

Protecting identities

In social-behavioral research, the greatest threat faced by undocumented participants is the threat that government officials will learn their identities and attempt to deport them.

So, researchers who actively recruit this population put much of their energies into devising means of protecting the identities of participants from eventual disclosure.

These methods vary from study to study, depending upon the researcher and how much information he or she needs. Berk and **Michele Shedlin**, PhD, a senior fellow at the Hispanic Health Disparities Research Center at the University of Texas, El Paso, both say that the privacy safeguards they include in their studies are extremely stringent, often going beyond the normal requirements of their IRBs.

The most common protection sought is a certificate of confidentiality issued by the National Institutes of Health. The certificate protects the researcher from having to release identifying information in response to a court order or subpoena.

According to the NIH, the legality of the certificate has been upheld in the courts, but some still worry about possible limits of its authority.

Berk, who has surveyed undocumented immigrants regarding their access to health care services, specifically asked participants their immigration status. When determining how to maintain the confidentiality of the data, Berk's group came up with an extreme solution — they destroyed all identifying data after they determined they had the information they needed.

"The IRB did not insist on that. We decided to do that," he says. "As we went into the field, we talked to people and learned what their risks were. We informed the IRB and they were fine with it."

Berk noted that his research was not government funded — it was funded by the Robert

Wood Johnson and Kaiser Family foundations, which he says gave him less protection against forced disclosure.

"I didn't want to run into a situation where a law enforcement agency in Texas would say, 'You've got a list of hundreds of undocumenteds, we'd like to have it,'" he says. "The only way to be absolutely sure that we wouldn't be in that situation was to destroy everything."

He notes that that approach precluded the possibility of conducting a longitudinal study with the participants. He says it's ironic that had the government funded his study, it would have strengthened the protections afforded participants — but he believes undocumented workers would have been less likely to trust a government-funded study.

Shedlin, who has studied HIV and substance-abuse issues, took a different approach when dealing with migrant farm workers in Long Island, NY. She did apply for and receive a certificate of confidentiality — "everybody needs to get that if they're working with undocumented community residents" — but she also limited the amount of personal identifiers she collected. In fact, she never specifically asked participants if they were in the country illegally, despite the fact that she knew most of them were.

"There's no question that a large percentage of these people were undocumented," she says. "We took no identifiers. We have demographic characteristics of our sample, but we did not ask for names. So there were no records to keep."

Shedlin says researchers and IRBs dealing with an undocumented population should think very carefully about how much information is really necessary for the research.

"It's something we all do, we always collect too much information," she says. "But if you don't need identifiers, then why collect it? That doesn't mean you don't collect information about who your sample is and what their characteristics are, but it does mean that if you don't need names and addresses, you don't collect them."

Taking care with incentives

Another thorny ethical issue in research with undocumented immigrants is the practice of offering incentives for everything from filling out a form to testing a drug.

Because the undocumented population can be extremely poor, the incentives can be a powerful force in a participant's decision to take on risks.

Berk notes that part of his research involved putting together focus groups of illegal immigrants to talk about their health care situation. Those involved in the groups were offered $40 to participate.

When the facilitator asked the group why they came, "they all said it was the $40," Berk says. "Some of them were quite worried that it was a [government] trap, but they weren't about to turn down the $40.

"A woman actually came with her suitcase. She wasn't willing to give up the money, but she thought the odds that this was a trap were so high that she had packed."

Berk sees an ethical challenge in crafting an incentive level that does not unduly influence a poor population, but adequately compensates them for their time and effort.

Shedlin agrees, saying she feels strongly that participants should receive incentives.

"They are collaborating on a research project and giving their time and spending carfare and these kinds of things — of course they should be compensated," she says.

She says community workers who spend a lot of time with the immigrants being studied should be consulted to arrive at a fair amount.

"Community-based organizations, (non-governmental organizations), hospitals — the people working with these populations — have a very good idea of what would be compensation and what might be coercive.

"It's a fine line, it's always a fine line," Shedlin says. "But in combination with all the other protections, I think you can work well to establish a fair compensation."

Biomedical risks

Conducting biomedical research with illegal immigrants adds a whole layer of risk, since immigrants who are not in the country legally could be constrained from reporting any unethical behavior or adverse outcomes.

But Shedlin notes that other vulnerable populations, such as drug users or non-English speaking legal immigrants, face some of the same obstacles to reporting problems.

The potential for exploitation was brought into sharp focus in Miami a few years ago when news reports alleged safety and ethical lapses by a private firm operating a clinical trial site in the city. Later stories alleged that immigrant subjects were threatened with deportation if they didn't

refute the charges in the earlier articles.

The company has since closed its Miami operation; the testing center was demolished after the county board deemed it unsafe.

Goodman says he doesn't believe exploitation of undocumented immigrants in research is a widespread problem, but he believes it deserves further study. He says some of the factors in the Miami case illustrate the obstacles faced in protecting immigrants and other vulnerable populations.

"I want very much to believe that people running clinical research projects would not threaten someone with deportation because they chose to exercise their rights to communicate," he says. "I believe it's an aberration, although it's an aberration borne of the idea that a lot of these Phase I trials need to be farmed out to for-profit corporations."

When he visited the site, Goodman says he saw participants — not all of them in the country illegally — approach a window and ask "What [studies] do you have for $2,500 today?"

"IRBs, especially IRBs at academic medical centers, are accustomed to a much more genteel process," he says. "The idea that an advertisement would draw people off the street who were there shopping for protocols was a real eye opener — and a real source of concern."

While IRBs need to be attuned to the vulnerabilities of this population, Goodman says it shouldn't be a reason to close off research to undocumented immigrants.

"Depending on the research, it might very well be the case that including undocumented immigrants as subjects would be a way to improve health care for undocumented immigrants," he says. "To be sure, it's a vulnerable population, but we've got some experience with managing vulnerable populations — protecting their rights, protecting their interests, and so forth. And through mechanisms such as certificates of confidentiality and robust IRB review, we've been able to see our way clear to do research, which I believe on balance helps this population." ■

Data protection, informed consent are key for illegals

IRBs should be flexible, seek out expertise

As IRBs review research proposals that may include illegal immigrants — or even recruit them outright — those who work with this population say there are a number of issues boards should consider:

- **Protection of data** – Because of the risks of disclosure, IRBs should insist on the tightest possible protection of records, particularly those that may contain identifiers. Certificates of confidentiality should be sought to protect records from the threat of subpoena or court order.

And Shedlin notes that it's not always necessary to collect incriminating data. "If you don't need identifiers, don't collect them."

- **Informed consent** – The consent process can help assure prospective participants that their information will be protected, says **Ken Goodman**, PhD, director of the Bioethics Program at the University of Miami in Miami, FL. That, in turn, decreases the risk of exploitation, since participants know they're safe from exposure.

"You say explicitly that come what may, you're not going to be reported to the immigration authorities," he says. "People who are outside of this study are not going to have access to the records."

The informed consent process itself can be intimidating to immigrants, particularly those from countries with authoritarian governments, says **Michele Shedlin**, PhD, a senior fellow at the Hispanic Health Disparities Research Center at the University of Texas, El Paso.

"They come from an environment where these things are not done, and there's certainly no understanding of research," she says. "You win enough confidence and rapport for people to agree to do an interview, and then you read them this long, legally mandated, complicated thing, and they freak out.

"They ask, 'What is this government document? Why do we have to sign this?' Sometimes it takes a very, very long time and a very careful explanation."

Shedlin says this can add substantially to the length of the consent process, but is vital to ensure that participants understand how they are protected.

And, of course, as with all populations that are non-English speaking, consent forms must be in the appropriate languages.

Give investigators flexibility

- **Flexibility** – Researchers may need to deviate from planned methodologies or consent procedures in order to address risks as they learn about them. IRBs should be ready to weather

those changes as well, say **Shedlin and Marc L. Berk**, PhD, senior vice president for health policy and evaluation at the National Opinion Research Center at the University of Chicago, Chicago IL.

Berk says his interviewers dress far more casually than they do for other surveys in order to put respondents at ease. They're also given leeway to deviate from the script when necessary to build trust.

Shedlin says that as an anthropologist, she does initial exploratory field work on her studies, which can lead to changes. She cites an example, not involving illegal immigrants: While surveying homeless women in a welfare hotel in New York, she learned that drug dealing was rampant in the building, and that women would be coerced into participating through threats that their children could be taken away by authorities.

So she scrapped plans for focus groups in which women were to discuss their difficulties obtaining pediatric health care, since the discussions might expose vulnerabilities that could be used against the women later. Women were interviewed individually instead.

"I reported back to the IRB why the methodology changed," Shedlin says. "These are the kinds of things that you tailor to vulnerable populations in response to specific vulnerabilities. An IRB can't always know them ahead of time and, sometimes, neither can the investigator until they're in the field."

• **Financial incentives** – Researchers advise IRBs to be sensitive to the financial incentives offered to illegal immigrants, since some face severe financial hardships and could be unduly influenced by large payments.

Legality of incentives

There is a legal aspect to financial incentives as well. Many researchers working with undocumented participants provide incentive payments in cash to avoid having to identify recipients by name.

When asked whether payment for a study would be considered illegal "employment" under federal law, the response from the U.S. Citizenship and Immigration Services (formerly the Immigration and Naturalization Service) was less than clear.

"This is the kind of relationship that can be said to be on the margins of 'employment' because it is not what we normally think of by that term," according to the response from the USCIS counsel's office. "However, the regulatory definition of employment is quite expansive, and does include many relationships that may be short term or different in other ways from the more classic salaried or waged position type of employment."

Sonal Ambegaokar, a health policy attorney with the National Immigration Law Center in Los Angeles, CA, says she believes institutions and researchers aren't putting themselves at undue risk by providing incentive payments to research subjects.

"I would see it as compensation, but I don't think it's an employment relationship," Ambegaokar says.

• **IRB membership** – Shedlin says IRBs that deal with studies involving illegal immigrants should include members who understand the unique vulnerabilities of the population.

"People who have either worked in areas of immigration and migration, people who have worked in the countries involved, who know something about where these folks are coming from," she says. "Many of these people have gone through horrendous trauma and hardship and violence in getting here. Not only are they new immigrants and may be undocumented, but they may be suffering from post traumatic stress disorder, as well as other issues.

"I think it's good for IRBs to have some orientation about the issues of these populations, not just whether they're legal or not legal," she says.

• **Local laws** – In the past few years, states, and even municipalities, have passed laws and ordinances restricting dealings with undocumented immigrants. Shedlin says individual IRBs should be alert to any changes, as well as possible implications for research.

"We need to be very aware of what the changes are in the laws, so that we protect our institutions and researchers and participants," she says. "We don't want to do things that aren't legal, obviously." ■

Possible OHRP guidance could come this year

HHS, other agencies must approve draft first

Does the Office of Human Research Protections (OHRP) plan to release guidelines this year clarifying what is and isn't research requiring IRB review?

Apparently, the answer is an unqualified "maybe."

In an interview in February with *The New York Times*, ORHP Director **Bernard Schwetz**, DVM, PhD, hinted that new guidance might be forthcoming this year.

The article discussed the continuing tensions between IRBs and researchers in disciplines such as anthropology and oral history. Researchers in these areas have long complained that IRBs have unnecessarily intruded into studies that were not true research, with burdensome and time-consuming requirements — a phenomenon they describe as "mission creep."

Schwetz acknowledged that guidelines for IRBs weren't clear enough. *The Times* reported that he said new guidelines would provide better examples to help IRBs determine whether a proposed study qualified as "research" under the Common Rule.

However, in an interview with *IRB Advisor*, Schwetz says a 2007 timeline for new guidance on this contentious issue is dependent on many factors, none of them a sure bet.

'Go' or 'no go'

Schwetz described a process with several "go" or "no go" steps, any of which could derail the planned guidance:

• Currently, the draft proposal is being discussed within the agencies of the U.S. Department of Health and Human Services, which includes OHRP.

"We're trying to determine if we're going to be able to reach agreement on what this guidance would look like within HHS," Schwetz says. "If, in fact, we find that there are some significant things that we have to work on before we could ever reach agreement on a guidance, then we would essentially retreat and work on those."

Schwetz says he hopes that decision — to retreat or go forward with a proposed guidance — could come in the next few months.

• If the guidance does pass this point, then it still would have to be reviewed by the other agencies bound by the Common Rule.

"That, again, is a process where we often get a fairly wide divergence of opinions," Schwetz says. "So, it likely would be several additional months before we would get some reading on what other agencies have told us to do and whether we can satisfactorily respond to their comments."

• If the proposed guidance continues to be a "go," Schwetz says it's possible that it could be available for public comment by the end of this year.

Divergent views

Part of the difficulty in shepherding this proposal along is the sheer number of agencies that must review it, Schwetz says. He says there are divergent views among this group as to whether a new guidance would even be advisable.

The studies in question occupy a gray area between research that clearly warrants IRB review and academic activities that obviously don't constitute research and so don't need the input of an IRB. Trying to clarify the research definition will inevitably cause some researchers to disagree with the results, Schwetz says.

"It isn't our intent to create a lot more burden," he says. "On the other hand, there are people who want this to be clarified because they don't like the feeling of possibly operating outside of compliance — or operating with compliance when they didn't need it."

The controversy over what constitutes research under the Common Rule isn't a new one, Schwetz says.

"I remember talking to some of the people who have been the leaders in the human subject protection community for decades saying this was an issue 20 to 30 years ago," he says. "Ever since the regulations have been out there, and even before, people have argued about whether something is research or not.

"In fact, we were advised by some of them, don't take this on because you'll never get an answer."

For his part, Schwetz isn't sure whether the issue will be resolved this year. But he's willing to take it slowly, noting that the studies involved don't represent a large degree of risk to participants.

"Because we hear fairly divergent views on it, we're going slowly to make sure we don't have to retreat and do something different," he says. "I don't want to do this twice. If we're going to do it, I want to do it once — right." ■

Industry has grown to accept CT registries

Lack of legislation has not stopped their spread

The clinical research community has begun to accept the presence of clinical trial registries, despite lingering questions about intellectual property rights and other issues.

Since the benefits of having research transparency might outweigh the harms, some experts wonder why IRBs do not use their oversight power to promote clinical trial registration.

Registration affords investigators the opportunity to use the registries, as well as literature reviews, as part of the explanation for why a particular study is needed, says **Alexander M. Capron**, LLB, professor of law and medicine, Scott H. Bice Chair in Healthcare Law, Policy, and Ethics, and co-director of the Pacific Center for Health Policy and Ethics at the University of Southern California in Los Angeles, CA. Capron spoke about clinical trial registries and databases at the annual conference of the Public Responsibility In Medicine & Research (PRIM&R), held Nov. 15-19, 2006, in Washington, DC.

"It would seem to me it would be beneficial for research ethics committees to be supporters of the use of clinical trial registries," Capron says. "It happens that nobody is in a better position to advance the use of clinical trial registries than IRBs."

IRBs had a huge impact on research in terms of forcing the research community to better explain itself, and they've made research better by spending time on the fine points of informed consent, Capron notes.

However, the question that is essential to an IRB's purpose is whether research is designed in such a way that it will produce results that are scientifically important and valid, Capron says.

"Since the IRB approval is needed before any trial can commence, research ethics committees could make a requirement that before a trial can be approved, they need notification from the investigator that the trial has been registered, and 'Here's the trial registry number,'" Capron explains.

To some, that idea might seem burdensome to IRBs.

When 50 representatives from the various research stakeholders met two years ago to discuss the future of pharmaceuticals, there were presentations about clinical trial registries and the common ground regarding all of the issues surrounding the topic, recalls **Celia Fisher**, PhD, director of the Center for Ethics Education and a Marie Ward Doty professor of psychology at Fordham University in New York, NY. Fisher also spoke about clinical trial registries at the PRIM&R conference.

"In the first draft of the Fair Access to Clinical Trials Act, IRBs were going to serve as gatekeepers and guarantee to the Food and Drug Administration (FDA) that indeed the research would be posted on a registry," Fisher explains.

"That seemed to be an undue burden on IRBs, who don't have enough money to begin with, and that's not their area of expertise," she adds. "So everyone agreed that it probably wasn't the best route to take."

Instead, the onus of proof that a trial is registered should come from the sponsor, Fisher says.

"It would be too costly and inefficient and unfair to burden IRBs with it," she says.

The stakeholders' sessions also raised questions about the purpose of registries and databases, Fisher notes.

When the International Committee of Medical Journal Editors (ICMJE) said they would no longer accept journal articles from studies that were not registered, the rationale was that there was some kind of bias for positive results in the published studies, Fisher explains.

This didn't mean a bias was intentional, but it existed, she adds.

"The science community basically sees studies that work and have significant differences," Fisher says.

So it would provide an additional check and balance to know about more of the studies that were conducted, she says.

"So if someone submits an article to the *New England Journal of Medicine (NEJM)*, then *NEJM* editors can go back to the registry to see how many of these studies have been conducted," Fisher says. "It allows for peer review that is a little more sophisticated and has more knowledge about research in this area."

On the other hand, the journal editors' decision has only limited impact on registration because studies that lack positive results won't be published, and since they won't be published, the sponsor will not have to worry about registering them, Capron says.

"The purpose of the major journals, which are requiring clinical trial registries, is to have people register at the beginning of the trial, because if they don't do that, it doesn't do any good to do it at the end," Capron says.

Although legislation, called the Fair Access to Clinical Trials (FACT) Act, now in its third version before Congress, includes registry requirements, it is unlikely it will be passed soon, Capron says.

"It seems to me it is much more likely that if the IRBs at leading institutions start saying, 'Yes, this is a part of our process that we expect,' then we'll have the change and, eventually, it will make its way into a regulation," Capron says.

The next question regarding registries has to

do with how much information should be included and how it should be used, Fisher says.

At the government-funded Web site: www.ClinicalTrials.gov, anyone can search for clinical trials about a particular topic and find a list of hundreds of ongoing trials. For example, a quick search under the topic "skin cancer" reveals 953 clinical trials, almost all of which are recruiting subjects.

Investigators can register any trial that has been approved by an ethics review board and that conforms to federal regulations. Registration takes place via a Web-based data entry system called the Protocol Registration System.

The Web site conforms with requirements by the ICMJE and advises lead sponsors of multi-sponsor trials to take responsibility for registration.

This type of registration provides patients with greater access to clinical trials, but that's only one aspect of registration, Fisher says.

Opening registries to more information could raise intellectual property rights questions, she says.

For example, how do you protect the rights of a company that is developing a new medication but does not want competitors to know?

"Before a product is FDA-approved or marketed, it may be necessary to protect the name of the sponsor, the name of the drug, and aspects of the ingredients," Fisher says. "So with that kind of research, it could still be required to be registered, but it would be company X or product X."

Later, the registry information would become available when the researchers submitted an article to a journal, giving the journal permission to look inside this lock box registry, Fisher explains.

Eventually, all of the information would be made public.

"So that was one of the things I thought was a nice combination of stakeholder interest in protecting intellectual property rights, and public interest," Fisher says.

Another issue involves the publication of databases that include all of the trials, including "good" and "bad" studies, Fisher says.

"The public doesn't have the scientific education to determine what's good or bad," she says. "What would be seen as a legitimate site in which they could review data, as well as know whether or not this study is based on a sample size that is small?"

It's not that some companies engage in unethical research, but some research simply cannot be generalized, so how could a database sponsor protect against misinterpretation and findings that appear more efficacious than they are, Fisher asks.

For example, critics of the FACT Act have said that it would be difficult to evaluate trial information included in a database, she says.

"If the company itself was required to interpret it, there would be other legal issues that would arise," Fisher says. "There would have to be non-promotional language in the database."

Also, could all of the audiences that a database serves be well-served with one database?

"I think it's a great idea, but it could really backfire if it's not done right because there would be no peer review," Fisher says. "Do we want something like Wikipedia, which is a consumer-beware site where you don't know what's right or wrong?"

Physicians and others are concerned about liability issues with a large database of trials. For instance, would a physician then be expected to check this database for every trial ever conducted for a new drug before prescribing it?

"They neither have the time nor expertise to go through that much information," Fisher says. "That's why we have medical journals, because there's a guarantee that scientists can draw upon that information." ■

COMPLIANCE CORNER

Expert offers advice on investigator noncompliance

Institutional involvement is crucial

Research compliance can be defined a variety of ways, and the trick is for institutions to define and understand the types of noncompliance that are reportable to federal agencies, a compliance expert says.

"There are various levels of noncompliance from scientific misconduct to minor administrative oversight to serious noncompliance," says **Heather L. Fields**, JD, a shareholder in the health care department of Reinhart, Boerner, Van Deuren of Milwaukee, WI. Fields speaks at national IRB and research conferences about compliance and other issues.

The Food and Drug Administration (FDA) and the U.S. Department of Health and Human

Services (DHHS) require IRBs to report serious or continuing noncompliance with DHHS or FDA regulations or IRB determinations, Fields notes.

Noncompliance also should be reported to the research institution and the study sponsor.

Federal regulations leave it up to each institution and IRB to define the words "serious" and "continuing."

However, Fields offers these examples of continuing noncompliance, serious noncompliance, and scientific misconduct:

• **Continuing noncompliance:**

The principal investigator (PI) repeatedly fails to keep complete temperature logs in compliance with the protocol-specific storage and handling plan for an investigational test article; or

The PI repeatedly fails to file adverse event reports with the IRB in a timely manner.

• **Serious noncompliance examples:**

The PI conducts non-exempt human subjects research without having obtained appropriate informed consent and without IRB review and approval; or

The PI makes a significant modification to the IRB-approved research protocol (e.g., increases dosage amounts) without first obtaining IRB approval.

• **Scientific misconduct:**

Fabrication: When a PI makes up data or results and records or reports them;

Falsification: When a PI manipulates research material, equipment, or processes, and/or changes or omits data or results; or

Plagiarism: When a PI uses another person's ideas, processes, results, or words, and doesn't give the original source credit.

Typically, reports to OHRP and the FDA will include these items, Fields says:

• Name of the research institution;
• Name of the PI;
• Name of the research project and/or grant proposal;
• Number of the research project;
• Description in detail of the noncompliance; and
• Corrective actions being taken by the institution.

Another issue that is left up to the institution's discretion is the precise time frame for reporting noncompliance, Fields says.

"The new guidance from the Office of Human Research Protection (OHRP) provides a time frame that is hard to pin down because the regulations require prompt reporting, but don't give a date, she says.

"What OHRP will tell you is that depending on the seriousness of the incident, they want to know within a few days to a few weeks," Fields says. "If 30 days have gone by and you have not reported it, then that's a problem."

The clock starts ticking when the institution becomes aware of the incident, but this can be tricky, as well.

For instance, an IRB might hear an allegation from a study nurse that something's wrong, but it takes time to sort out whether the allegation is credible and to find out what's really going on, Fields explains.

When Fields offers examples, she'll say that a single, late adverse event report that was lost on someone's desk may not be serious, and is not continuing.

"But if they repeatedly fail to file reports they are required to report, or if they repeatedly refuse to address the IRB's request for information, or are not filing continuing review reports, then that may eventually rise to the level of something that needs to be reported," Fields explains.

Protocol changes without IRB approval are another area of noncompliance, and the severity of these can range from minor to serious.

"There are a fair number of PIs out there who will modify what they are doing with a research study, and they may not seek an amendment to the protocol," Fields says.

"Suppose there is a PI who modifies a study drug's dosage for a single patient because the person is not tolerating the levels of doses called for, then obviously the PI can make modifications to protect the patient's health and safety," Fields explains. "But that must be reported as a protocol deviation, and if it continues to be an issue, the protocol may need to be modified."

"The most important thing for IRBs to understand is their role in the institution's compliance process," Fields says. "I don't think IRBs are well-suited to handle noncompliance investigations or to sort out all of the facts that need to be detailed."

It's the research institution's responsibility to make certain subjects are protected, and so it's important to have someone at the institutional level be in charge and responsible for any investigation into research noncompliance, Fields adds.

"It's critical that the IRBs are alerted to noncompliance, and they do make the required reports, but it doesn't mean they have to be in charge of the process," Fields says.

The institution's compliance process needs to encompass a variety of offices dealing with

research projects, including the financial office, the grants office, the dean's office, and the IRB office, Fields says.

Fields offers these suggestions for how an institution should handle noncompliance issues:

- **First:** Identify someone to lead the institutional process (the IRB staff and members may not be best situated to take charge of this process);
- **Second:** Conduct at least a preliminary investigation to find out what type of noncompliance is involved;
- **Third:** If serious or continuing (or suspected to be serious and continuing) noncompliance occurs, then report to appropriate departments within the institution and have the IRB report to the required governmental agencies;
- **Four:** Complete the full investigation of the specific incident, looking for patterns of continuing noncompliance (audits could be used to determine if it's an ongoing problem);
- **Five:** Develop a corrective action plan to address the investigation's findings; and
- **Six:** Provide follow-up, including making additional governmental reports and monitoring implementation of the corrective action plan.

"You need to ferret out the problems and investigate them with the ultimate goal of preventing future problems by educating and training the entire research staff," Fields says.

In an ideal situation, a noncompliance finding would result in an institution providing additional support to the investigator and research staff and offering education and training to enhance their understanding of compliance issues, she says.

"Also, you need to have a system in place that has lots of safeguards to make sure people know what they're supposed to be doing," Fields explains. "And you need to make sure there's a process to catch problems early before things become serious."

Fields offers these examples of types of corrective action that could be taken in response to noncompliance:

- Modifying the consent form or the research;
- Notifying current or past study participants;
- Providing another informed consent of current participants;
- Monitoring research and consent process;
- Educating and mentoring PIs and study staff;
- Providing more frequent reviews and additional reporting;
- Making additional resources available to support the PI's activities;
- Placing limitations on the PI's research activities or use of data; and
- Suspending or terminating IRB approval.

Education and training are an institution's and IRB's best defense against noncompliance problems, Fields says.

Quality improvement programs and random audits are some of the ways an institution can prevent noncompliance crises.

"Do a spot check to help research staff before they do something that becomes a significant noncompliance issue," Fields suggests.

This effort will pay off in the end because the goal is to help improve the lives of research subjects and move forward medical thinking, Fields says.

"It's very time-consuming and expensive for institutions to deal with serious noncompliance," Fields adds. "It's an integrity issue, and it causes a lot of disruption in the day-to-day operations." ■

Survey offers insight into informed consent

Very few were aware of PolyHeme study

A recent study suggests that emergency medicine patients may not have a high level of acceptance of the practice of providing an exemption to informed consent for research involving emergency medical settings.[1]

"We looked at nearly 500 patients who presented to the emergency room and who were not critically injured, and we queried them on their attitudes and beliefs about having an exception to informed consent," says **Wayne Triner**, DO, MPH, FACEP, an associate professor in the department of emergency medicine at Albany Medical College, and a senior fellow at the Alden March Bioethics Institute in Albany, NY.

"We found that, by and large, patients agreed with the notion that research of this nature, with a waiver for informed consent, was important to do, but they had issues with such research transpiring among themselves or family members," Triner says.

About one-third of those surveyed said they would be willing to have themselves or family members participate in such a study, and one third strongly disagreed, while about 80 percent of participants agreed that such studies need to be done, Triner says.

Investigators pointedly did not survey people

who were involved in a research project.

The study took place after there were some general media reports about concerns over the enrollment and disclosure practices of the PolyHeme clinical trial, which was sponsored by Northfield Laboratories Inc. of Evanston, IL.[1]

PolyHeme is an oxygen-carrying resuscitative fluid designed for use in urgent blood loss when blood isn't immediately available. During clinical trials, some patients receiving the product died of heart attacks, which raised questions about the waiver of informed consent.

The trial was conducted with informed consent waivers because of its use in emergency, life-threatening situations. Community education was conducted prior to the trial's initiation, and the public was offered a way to opt-out of inclusion.

"We specifically did this after the PolyHeme study," Triner says. "We thought the emergency department patients were the best surrogate for actual patients to be enrolled from this population."

Researchers asked participants about the PolyHeme study, and found that awareness of the study was very low prior to the media scrutiny, Triner notes.

About half of the participants were surveyed after widespread media reports involving PolyHeme, and participant awareness remained low, he adds.

"The number of people reporting awareness was approximately 8 percent," Triner says.

About half of this number knew any specifics about the trial, he adds.

"Many previous studies that investigate community acceptance of waivers of informed consent in studies have all been done at community meetings, and there's a selection bias of who goes to these meetings," Triner says. "There are several articles showing nearly unanimous acceptance of waivers of informed consent among people who attend these meetings."

The acceptance was considerably lower among the emergency room patients, Triner says.

"We think that more closely matches the actual population," he adds.

The survey's results raise questions about the use of opting out in such waiver cases.

"Intrinsic to the regulations surrounding those studies, people had to sign up if they didn't want to be enrolled in the emergency research," Triner says. "If only 4 percent of the population affected by the study is even aware the study exists, then how do the majority of people know to opt out?"

Alternately, opt-in registries would be impractical for researchers, he says.

"What happens is you're not going to reach a significant proportion of the population eligible for enrollment, and if you did reach them, they'd have to exercise the intent and actively enroll themselves on that registry for that particular study," Triner explains. "So from an investigator's standpoint, you would not enroll anybody, and you'd have very limited opportunity to enroll patients."

This creates an interesting dilemma for IRBs, who have to weigh the potential benefits against potential risks and individual rights, Triner notes.

"I think we need to clarify social benefits versus

CE/CME Objectives

The CE/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

- Self experimentation: What IRBs should know
- Educating staff about IRB guidelines
- Experts discuss HIV/AIDS research in poor regions
- Write better standard operating procedures
- Improve continuing review process

individual rights and risks, and there may be situations or conditions where it's more important to do the study," he adds.

"We're in an era of finding strong evidence to justify or reject the things we do in medicine," Triner says. "We have a long history of embracing innovations in medicine based on case history, but the strongest evidence is randomized trials."

In the big picture, it's important that resuscitation research continue so medical providers will have evidence on which to base emergency medical decisions, Triner says.

"I hope IRBs don't reach the point of not approving waivers for informed consent," Triner says. "What our study highlights is that for the short term they need to consider how these studies are being initiated and how the notification of affected populations is being brought into the process."

This would require genuine community representatives being engaged in the process and identifying formal and active community leaders, Triner says.

"As an emergency room practitioner I firmly believe that these studies are essential," Triner adds. ■

Reference:

1. Triner W, et al. Exception from informed consent enrollment in emergency medical research: attitudes and awareness. *Acad Emerg Med*. 2007;14:187-191.

CE/CME *questions*

19. True or false: A certificate of confidentiality protects a researcher from having to disclose identifying information about subjects, even if presented with a court order or subpoena.

20. In order to protect identifying data when working with illegal immigrants, a researcher may:
A. Obtain a certificate of confidentiality
B. Destroy identifiers after use
C. Decide not to collect identifiers
D. All of the above

21. The U.S. government's Web site for clinical trial registries (www.ClinicalTrials.gov) permits registration of trials that have met which of these standards:
A. Approval by an ethics review board and conformity to federal regulations
B. Approval by an IRB and sponsored through federal funding
C. The study must be conducted by a previously-published investigator
D. None of the above

22. Which of the following is an example of scientific misconduct?
A. Fabrication - when a principal investigator makes up data or results
B. Falsification - when a principal investigator manipulates research material, equipment, or processes
C. Plagiarism - when a principal investigator uses another person's ideas, processes, results, or words and doesn't give the original source credit
D. All of the above

Answers: 19. (True); 20. (d); 21. (a); 22. (d)