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Your Practical Guide To Institutional Review Board Management

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IN THIS ISSUE

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Clinical trial participant's suicide raises ethical questions for IRBs

Conflict of interest and informed consent issues pondered

A recent legal case involving a clinical trial participant who committed suicide raises a variety of questions for IRBs.

The case stemmed from a clinical trial comparing antipsychotic medications used to treat schizophrenia. Twenty-seven-year-old participant Dan Markingson killed himself about six months into the trial.

Markingson's mother, Mary Weiss, sued the researchers, research institution, and pharmaceutical company after his death in 2004. Earlier this year, a judge ruled that the university had statutory immunity and that the drug company (AstraZeneca of Wilmington, DE) was in the clear because there was no convincing evidence that the drug caused the participant's death. The mother settled with the researcher for $75,000.[1] **(See timeline for Markingson case, p. 87)**

While there have been fewer shockwaves in the clinical trial industry from this case than there were years earlier when Jesse Gelsinger died during a clinical trial, it still highlights ethical concerns about conflicts of interest and informed consent of people with limited decision-making capacity.

In the Markingson case, the study's investigator was also the clinician who diagnosed the young man with schizophrenia, determined his ability to make an informed consent for the study, and decided whether he needed to be placed in an inpatient unit. Weiss had charged that the PI's decisions were made for the convenience of keeping her son in the clinical trial and not an objective determination of what would be best for him medically.[1]

Weiss also claimed that her son was never mentally sound enough to make adequate informed consent for participation in the research.[1]

Recognizing this issue as an ongoing concern, the Department of Health and Human Services' Secretary's Advisory Committee on Human Research Protections put on its July 15, 2008, meeting agenda a report from the subcommittee on the inclusion of individuals with impaired decision making in research. *[The meeting was held after* IRB Advisor's *deadline for this issue.]*

So *IRB Advisor* asked IRB and research ethic experts to discuss how IRBs could do a better job of protecting research participants, especially when they are part of a vulnerable population. **(See article on conflicts of interest, p. 88.)**

"There are a couple of very good resources for considering the ethics related to research with patients with diminished capacity," says **Don E. Workman**, PhD, interim associate vice president for research operations at Northwestern University in Evanston, IL.

Workman calls it a teeter-totter issue: "On one hand, there are times when people have diminished capacity, and you still need to respect their autonomous decision making," Workman says. "On the other hand, there are people with diminished capacity who need additional protections."

Decisional capacity is a difficult concept to fully understand, Workman notes.

"Do you give a mini-mental status exam and look at the score to see if people are able to consent?" he asks. "It's a gross marker, and we have to be careful about substituting its results for a clinician sitting down and speaking with a patient."

Even in patients with schizophrenia, there are times when these people are as capable of making good decisions as anyone else, he says.

Labeling different people "vulnerable" for research recruitment purposes may not be the most useful of strategies, says **Mark S. Schreiner**, MD, associate professor of anesthesia in pediatrics at the University of Pennsylvania in Philadelphia, PA. Schreiner also is the chair of the Committees for the Protection of Human Subjects at The Children's Hospital of Philadelphia and a member of the editorial advisory board for *IRB Advisor*.

People recruited for trials when they are experiencing economic hardship are vulnerable, as are people with terminal illness, Schreiner says.

"I can make a case why everyone is vulnerable in some way," he adds.

The best criteria for whether a person has the capacity to provide informed consent is this question: "Does the patient understand the risks and benefits of participating in research, and does the patient understand they have the option to not participate?" says **John Csernansky**, MD, Gilman professor and chairman in the department of psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine in Chicago, IL.

"There are a variety of different ways to evaluate capacity," Csernansky says. "But basically the concept of evaluating capacity relates to having a dialogue and discussion with the patient where the patient is not passively sitting and listening, but is asking questions and engaging in the informed consent process."

Through active listening, a researcher can determine whether a patient is asking for clarification in a way that will help the prospective study participant to best understand their role

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• *Fax:* (800) 284-3291 • *E-mail:* stephen.vance@ahcmedia.com
• *Address:* 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: **Suzanne Koziatek** and **Melinda Young**.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Associate Publisher: **Coles McKagen**, (404) 262-5420 (coles.mckagen@ahcmedia.com).
Senior Managing Editor: **Paula Cousins**, (816) 237-1833, (paula.cousins@ahcmedia.com).

Editorial Questions

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and responsibilities in a clinical trial, he adds.

Researchers can use tools to determine a potential participant's capacity for making informed consent, and some studies rely on these when the study population has been diagnosed with a mental illness. For example, the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is sometimes used for this purpose.[2,3]

Whether a researcher uses this tool or another one for determining decisional capacity, use of the tool and informed consent process needs to be well-documented, says **Alan M. Sugar**, MD, chairman of the New England Institutional Review Board and a professor of medicine at the Boston University School of Medicine in Boston, MA. Sugar is a member of the editorial advisory board of *IRB Advisor*.

"We certainly require that competency be documented so if the principal investigator/doctor says the person is competent, you'd expect that to show up in the medical record as a primary clinical determination," Sugar says. "Preferably, you'd have why the person was [deemed] competent in the source document."

Another avenue IRBs might pursue is to require studies to use patient advocates, who would advise potential study participants about their informed consent decision, particularly when potential participants' decisional capacity might be in doubt.

IRBs could request that patient advocates be used when a study appears to warrant such a measure, Csernansky says.

"I've chaired a committee meeting where an advocate was necessary for a given study," Csernansky says. "And I've also been a principal investigator of a study where an IRB asked me to have an advocate present."

"In general, this is a good approach for some studies — and not just for research with patients with psychiatric disorders, but also for a variety of disorders where patients are vulnerable," Csernansky says.

Other possibilities might be to have surrogate decision makers or family members present during the informed consent process, but these could pose problems, as well, the experts note.

"We have had studies with surrogate decision makers, and in the amazing perspective of time, the decisions made were contrary to what the people would have wanted," Schreiner says. "But at least it was somebody looking out for the subjects' interest."

If researchers were to have family members serve as surrogates or at least be present during informed consent for potential study participants

Timeline of Markingson's involvement with CT

- **Fall, 2003:** Mary Weiss convinced her son Dan Markingson to return home to Minnesota where she could seek treatment for his apparent psychiatric illness.
- **Nov. 12, 2003:** Markingson was taken to Regions Hospital in St. Paul, MN, but was quickly transferred to the University of Minnesota Medical Center in Fairview, MN.
- **Nov. 14, 2003:** Psychiatrist Stephen Olson, MD, recommended that a Dakota County District Court commit Markingson to the state treatment center in Anoka because of Markingson's delusions.
- **Mid-November, 2003:** Olson changed his mind and told the court that Markingson had begun to acknowledge his need for treatment.
- **Nov. 20, 2003:** A judge required Markingson to follow Olson's treatment plan.
- **Nov. 21, 2003:** Markingson signed an informed consent document to be a volunteer in the antipsychotic drug study, called Comparison of Atypicals for First Episode (CAFÉ). He also signed a hospital discharge plan that told him to follow Olson's instructions, take his medication, and attend CAFÉ study appointments.
- **Winter, 2003/2004:** Markingson received quetiapine fumarate (Seroquel®).
- **Dec. 8, 2003:** Markingson was transferred from the hospital to a halfway house.
- **Winter, 2004:** Weiss wrote Olson and Charles Schulz, MD, head of the University of Minnesota's psychiatry department, about her concerns regarding her son's continued delusions, and she requested that they consider different treatment options for Markingson. She considered but did not achieve legal guardianship.
- **May 8, 2004:** Markingson killed himself with ritualistic mutilation involving a knife. An autopsy found no quetiapine in his system.

Source: Olson J, Tosto P. Dan Markingson had delusions. His mother feared that the worst would happen. Then it did. *St. Paul Pioneer Press* May 23, 2008. Available at: www.TwinCities.com. ■

who are mentally ill, then there could be privacy regulation issues, particularly if the participant doesn't want anyone else involved.

"From an autonomy standpoint, HIPAA, for instance, might preclude the physician from commenting or communicating with a subject's mother without her son's permission," Workman says. "If I have a 27-year-old patient, my responsibility is to the patient and only to the patient, and only if the patient is unable to make decisions on his own would I consider overriding his interest."

If a potential research subject in a schizophrenia drug trial doesn't want a family member involved, then the issue for the investigator is how to judge whether the potential subject has the capacity, and not just the legal ability, to consent, Schreiner says.

"They need to have the capacity to protect their own interests," he says. ■

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Conflict of interest issues raised by subject's suicide

Subject's mother sued based on COI

When is the dual role of physician/investigator a conflict of interest? This is the question IRBs might consider in the aftermath of clinical trial participant Dan Markingson's suicide.

Conflicts of interest among physician investigators are on a lot of IRB members' minds as the U.S. Senate has held hearings on the matter, says **Mark S. Schreiner**, MD, an associate professor of anesthesia in pediatrics at the University of Pennsylvania in Philadelphia, PA. Schreiner also is the chair of the Committees for the Protection of Human Subjects at The Children's Hospital of Philadelphia.

Earlier this year, Sen. Chuck Grassley (R-Iowa) and his staff investigated payments made by drug companies to three psychiatrists/researchers, employed at Massachusetts General Hospital in Boston, MA. Grassley then called for a national reporting system that would track payments made by the drug industry to researchers.

Both the Markingson case and Grassley's investigations highlight how important it is for IRBs to be aware of any perceived or actual conflicts of interest among investigators.

Perhaps in response to both instances, AstraZeneca of Wilmington, DE, announced in May, 2008, that the company supports the revised Physician Payment Sunshine Act that Grassley and Sen. Herb Kohl (D-Wisconsin) sponsored. The act would create a national registry of payments made to health care providers and medical organizations by biopharmaceutical companies, medical supply companies, and device manufacturers.

Mary Weiss, Markingson's mother, claimed in a lawsuit that the investigator of her son's trial had a conflict of interest because of his dual role as her son's primary physician and an investigator in the study. The same person who diagnosed her son with schizophrenia also determined that he met the enrollment criteria and that he had the decisional capacity to understand that he could receive treatment whether or not he participated in the clinical trial. Weiss also claimed that the investigator's five-figure payment for each subject's enrollment created a conflict of interest.[1]

While it is debatable whether any particular payment per enrolled subject is considered excessive enough to be a conflict of interest, in general these payments are considered acceptable, Schreiner notes.

"Clinical trials are a huge amount of work," he says. "If you only paid people what they'd receive in clinical care then they'd never do research."

Also, there are many studies in which the primary physician is also the person who is conducting the clinical trial, Schreiner says.

"Parents of children in pediatric studies often agree to participate because the investigator is their physician, and they have trust in him," he says. "This is not a straight-forward issue."

The tradition of having physicians enroll patients in research protocols is a long and time-honored tradition that is done in a variety of medical fields, including oncology, says **John Csernansky**, MD, Gilman professor and chairman in the department of psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine in Chicago, IL.

"When I chaired an IRB it was commonplace to see protocols where physicians enrolled their own patients in research," Csernansky says.

"HIPAA regulations somewhat encourage this because these are patients who you can approach about research since they're your own patients."

If the question is whether a primary care physician should also be the principal investigator, the answer is both 'Yes' and 'No,' says **Don E. Workman**, PhD, interim associate vice president for research operations at Northwestern University in Evanston, IL.

"The reason for saying 'Yes' is that the physician knows the patient already and has the context and history from which to continue to monitor what's in the patient's best interest," Workman explains. "The reason for saying 'No' is that he may now confuse the two roles, and the patient may confuse the researcher as caregiver, and the physician might switch roles and treat the patient only as a subject."

So whenever there is a dual role, the physician/investigator needs to be cognizant of the dual role and manage it adequately, always recognizing that the patient is a patient first, Workman says.

Another strategy, particularly when a clinical trial involves a vulnerable population, would be to involve an independent second doctor to review patient care decisions.

"It's well accepted for principal investigators to be a person's doctor," says **Alan M. Sugar**, MD, chairman, New England Institutional Review Board, and a professor of medicine, Boston University School of Medicine, Boston, MA.

"The problem is exacerbated when people are vulnerable, such as psychiatric patients," he says.

"It's not the IRB's position to resolve the problem, but it needs to be discussed and solutions suggested," Sugar says. "One solution is having an independent, second doctor verify what the principal investigator/primary doctor wants to do, but there are some issues with that, as well."

For instance, the second doctor likely would be someone who works with the primary doctor, so there'd be a question of whether the second doctor's opinion was truly autonomous, he adds.

"The best thing is for the principal investigator to be separate from the person's physician, who then can act as the patient's advocate," Sugar says. "If there's any question, err on the side of caution and have other people participate." ■

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1. Olson J, Tosto P. Dan Markingson had delusions. His mother feared that the worst would happen. Then it did. *St. Paul Pioneer Press* May 23, 2008. Available at: www.TwinCities.com.

In rare instances, IRBs may need to go beyond regulatory framework

What's ethical might require planning, creativity

Sometimes IRB members will need to view a particular human subject research issue with more of an eye on what is the most ethical decision to make, as opposed to what is the best way to comply with rules and regulations.

"The issue is that the regulations provide the floor, but occasionally there are situations where there's a hole in what the regulations address or a context where the ethically sound thing to do is regulatory noncompliance," says **Don E. Workman**, PhD, interim associate vice president for research operations at Northwestern University in Evanston, IL.

While 99.9% of the time, the human subjects protection regulations address all ethical issues that might rise, there is that small minority of cases where they are inadequate, Workman says.

Sometimes, these cases involve an IRB's decision to not offer a waiver of consent because the regulations do not specifically address a research case in which the waiver would be necessary.

"We had one study in front of our IRB that wanted a waiver of informed consent in a trial that would randomize pregnant women in labor to get an epidural," Workman says.

"Occasionally, in the procedure they would have a wet stick where the cerebral spinal fluid leaks out of a small hole made when the anesthesiologist puts in the aesthetic agent," he explains. "A decision has to be made in one or two minutes, and it's a rare event, so researchers needed 1,200 women eligible for randomization in order to get 120 for the study."

The IRB reviewing the protocol would not accept the researchers' justification for waiving informed consent, saying the patients had a right to informed consent, Workman recalls.

"Since it would be impossible for the researchers to obtain informed consent from 1,200 women who come into the hospital in labor, they could not do the study," he adds.

So research that might have helped clinicians decide the best way to handle a rare medical emergency could not be conducted because of the IRB's literal reading of the regulations, Workman says.

Even the Office of Human Research Protection (OHRP) would argue that there may be times when interpreting the regulations allows for alternative decision making, Workman notes.

For example, there are social environments where there may be a high rate of HIV infection among young women, and their children are born with HIV infection, but the mothers do not want the fathers to know the babies are HIV-positive, Workman says.

"The mother may not know what the father's HIV status is," he explains. "So if the child is coming in for a clinical trial, the regulations would require the permission of both parents unless one is not reasonably available."

In this context, the father might be available, but the mother is not willing to jeopardize her social status with the father by letting him know about the child's and her HIV infection, Workman says.

"So how do you approve the participation of the minor in a trial with more than minor risk?" he says. "You can ask for a waiver, but that might not satisfy the problem."

IRBs can waive the consent requirement where there's a prospect of a direct benefit from the study, and that could be one answer to this dilemma, he notes.

The other issue is that young children sometimes are not aware they have HIV infection, and so how could researchers satisfy an IRB that requires assent for the trial, Workman says.

"Parents are reticent to let the child know they are HIV-positive because the child might tell someone else and that would be stigmatizing," Workman says. "That flies in the face of the reasonable assent basis."

Most IRBs will handle such ethical issues by asking their boards' regulatory experts or legal counsel to tell them what to do, Workman says.

"There are times when it's appropriate to ask what the state law is and follow that," he says. "Other times, the better thing to do is for the IRB to make an ethically sound decision, giving it reasonable thought."

Another problematic situation is when a study's subjects are recruited from a different cultural background in which there is no written language corresponding to the subjects' oral language, Workman says.

While rare, this has happened, he adds.

"So the family presents at the emergency room, and the language in which they're fluent doesn't have a written form, and someone needs to be enrolled in a clinical trial because it's the only available alternative," Workman explains.

Even if researchers use a short consent form, it has to be in a language that's understandable to the subjects, he says.

"So if the language doesn't have a written form, then there's no way to provide them access to the clinical trial," Workman says. "You could administer informed consent verbally, but you couldn't have written documentation of informed consent."

This also would be an instance when an IRB waiver wouldn't meet the criteria for waiver under current regulations, he adds.

What these unusual examples suggest is that there are instances where IRBs will have to think beyond the regulatory framework and look at making decisions that are ethical and will meet the law's intent of providing the best human subjects protection.

Sometimes IRBs have to make a decision that might not be explicitly addressed in federal, state, and local laws, Workman says.

For instance, in many states there are laws addressing when minors are emancipated, but they don't always address when they are emancipated for the purpose of participation in research, Workman says.

For example, in Illinois and some other states, the laws that address how and when minors might seek medical care without parental permission are not necessarily written with research studies in mind, he explains.

So an IRB that is reviewing a study that addresses environmental factors and the impact on premature babies, including babies who are born to mothers who are minors, could have a problem deciding whether the parents, who are minors, could ethically and legally give informed consent for the babies' participation, Workman says.

"And you can't go to the grandmother because the grandmother has no right to give consent, although she could give permission for medical care," Workman adds.

In these sorts of rare situations, an IRB might have to make an ethical decision that is not explicitly outlined in state laws and federal regulations, Workman says.

When such a case comes to an IRB, the IRB could always call OHRP and request guidance in thinking through the various ethical and legal issues, he suggests.

"If they encounter a situation where the

regulations don't apply, they should look to sources of the information, like regulatory experts in the room," Workman says. "But in absence of a clearly articulated regulatory or legal solution, they need to step back and make an ethical decision." ■

When clinical research turns up the unexpected

Anticipate incidental findings in every study

Researchers using magnetic resonance imaging (MRI) in a cognitive psychology study note a suspicious mass in the brain of a supposedly healthy volunteer.

A geneticist investigating the prevalence of a disease in a family discovers that one of the siblings being studied has a different father than the others — a fact the sibling is not aware of.

A researcher using archived genomic data discovers a potentially important clinical finding about a subject in a long-ago research project. The data were made anonymous, but the original researcher still has identifying information.

With the advent of revolutionary technologies designed to collect and analyze data, more researchers are being faced with problems such as these — so-called "incidental findings," or data generated about research subjects that go beyond the original aims of the study.

"It's really a product of the power of the technologies being used for research," says **Susan M. Wolf**, JD, a professor of law, medicine and public policy at the Center for Bioethics, University of Minnesota, Minneapolis. "Not only the technologies that generate the raw data — things like new imaging technologies — but also the increasingly sophisticated technologies we use to analyze those data: bioinformatics capabilities in genomics, for example, or new computer analysis techniques used to do fine-grained analysis of images.

"As we do more and more of that, it's really inevitable that we'll be faced with more and more extra data."

How to handle that extra data — determining what's important and what isn't, and whether and how to inform participants — has become an issue of growing concern to researchers and IRBs.

Most recently, Wolf was the principal investigator for a National Institutes of Health-funded project about incidental findings that resulted in a 17-article symposium published this summer in the *Journal of Law, Medicine & Ethics*.[1]

Wolf says that when she and her colleagues began looking at how IRBs handle incidental findings, they found little guidance for investigators and boards. In examining the top 100 NIH-funded universities, she says most IRB web sites didn't even mention the possibility of incidental findings. Among those that did, there was little consistency about how they should be managed.

In part that may be due to the varied types of findings that can occur in different research settings. Genetic and genomic research can reveal information about a person's possible susceptibility to disease, or can uncover family secrets such as misattributed paternity or undisclosed adoptions. Imaging research can uncover physical abnormalities, ranging from unimportant to life-threatening. Routine eligibility screening could uncover drug use or pregnancy.

In each case, the plan needed to manage the findings would be different, as each would raise different ethical and practical considerations. But Wolf says there always needs to be a plan.

"IRBs should be asking the incidental findings question about every study," she says. "What planning do they see in the protocol for handling incidental findings? Is the plan adequate? What are the plans for the consent process? Who, if anyone, is available to act as a clinical consultant on incidental findings? What are they going to do with this information?"

Different from research results: While incidental findings raise some of the same IRB issues as the return of research results to participants, Wolf says there is a difference.

In the case of research results, the investigator is likely the most knowledgeable person to inform participants about findings. But researchers who turn up incidental findings usually aren't studying the condition that's been uncovered and may know little about it. In those cases, a referral to an expert — a clinical geneticist, a neuroradiologist — may be necessary to know for sure if the finding is significant.

Even the technology used may not be optimized for diagnosing an unexpected finding. MRIs may not be of clinical grade, so a suspicious finding may require a second scan — potentially at the subject's expense.

While there are many elements to a good incidental findings management plan **(see article on the components of a management plan, p. 93)**, IRBs should keep several important points in

mind, say Wolf and others who study the issue:

• **Additional risks.** In addition to the risks of the procedure itself, the potential for incidental findings adds other risks for participants, says **Michael Hadskis**, LLM, assistant professor of law at Dalhousie University, Halifax, Nova Scotia, who has studied review boards' handling of incidental findings in MRI research.

Those can include the physical risks of the follow-up procedures required, the psychological risks of stress as the participant waits to find out if the finding is real and significant, and the financial costs of procedures as well as the potential impact on insurance.

"These are real risks, and they're not minor risks," Hadskis says.

• **Therapeutic misconception.** In the case of research involving MRI, for example, a participant could mistakenly believe that all scans are being reviewed by an expert in diagnosing abnormalities, or that the technology is optimal for diagnosing problems when it is not.

"The research subject might think, 'If there were something there, it would have been seen. I'm not told anything is there, therefore I'm healthy. And therefore, I'll ignore my headache,'" Hadskis says.

Wolf says a review of consent forms regarding incidental findings turned up a range of approaches to dealing with this problem.

"Some say, 'This is not clinical care — if you think there's something wrong with you, go to the doctor.' Others say, 'If we see something anomalous or something of concern, we are going to share it, with your permission, with a clinician and we'll tell you,'" she says.

Deciding when to tell subjects: Wolf says not all incidental findings necessitate giving information to subjects. A closer study of an initial finding may reveal that it's unimportant.

In genetic testing, results that indicate a non life-threatening condition that the subject can't do anything to address might not be revealed. Wolf says discoveries of misattributed paternity sometimes aren't told to subjects unless it's critically important.

One debate over incidental findings that continues is how to handle subjects who don't wish to be told about them. In some areas, such as genetic testing, a subject may feel that there is little he can do about the result and doesn't want the additional worry.

Complying with such a request is "absolutely recommended, in keeping with the long history in genetics and genomics of offering but not forcing information on people," Wolf says.

But in imaging research, where a scan could reveal an aneurysm about to burst or an aggressive but treatable brain tumor, there is more opposition to giving a subject the choice to "opt-out."

"I feel that that puts an investigator into a tremendously delicate situation, if a subject has signed off that they do not wish to be told, and an investigator by rare chance finds a medical problem that is treatable," says **Judy Illes**, PhD, an imaging neuroscientist and Canada Research Chair in Neuroethics for the National Core for Neuroethics at the University of British Columbia in Vancouver.

In fact, Illes says, she recently heard a suggestion that investigators use a subject's preference not to receive incidental findings as a part of the exclusion criteria for participating in a study. "I think it was a good idea, in fact."

Hadskis suggests IRBs evaluate each situation to determine whether an opt-out provision would be appropriate.

Archived data: If a researcher is using data from a previous study and analyzing them in a different way, then any individual results would, by definition, be incidental findings, Wolf says. In many cases, the data have been made anonymous and the subject is unreachable, but that's not always the case, she says.

"What if you find a really important incidental finding and the data are anonymous in the public databank on the web, but the original researchers could re-identify? Are there circumstances where you'd want to do that?"

She says that in any study where the results will be archived for later use, consent forms should address the potential for incidental findings well into the future.

Wolf says addressing the potential of incidental findings could add cost to some types of research, particularly when researchers would need to call in a consultant to review findings.

"The money has to be built into research budgets — we argue that that much is part of doing research responsibly," she says.

Illes says she doesn't agree with the concern of some that giving more IRB attention to incidental findings will result in studies being moved higher in risk, necessitating more lengthy reviews.

"What about recognizing the possibility of an incidental finding and expressing a management plan moves the risk position of a study? I don't think it does at all."

Hadskis says IRBs need to prepare for dealing with the issue by ensuring there's a member — or at least an ad-hoc member or consultant — who's familiar with the type of research being discussed, and the potential for incidental findings.

He says that as IRBs become more familiar with the issue, and best practice guidelines emerge, the process should become easier.

"I don't think you're going to have any sort of one-size-fits-all best practice guidelines," Hadskis says. "But I think well-crafted best practice guidelines are going to cover many situations. Some of these things won't be as big an issue as they are right now." ■

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Elements of an incidental findings management plan

Questions IRBs should ask

When the answer to the question of "Could there be incidental findings from this study?" is "Yes," experts agree that the protocol should include an incidental findings management plan.

What's in that plan could vary, depending on the type of study involved, and the nature of the findings, says **Judy Illes**, PhD, an imaging neuroscientist and Canada Research Chair in Neuroethics for the National Core for Neuroethics at the University of British Columbia in Vancouver.

"The management plan may rightfully take different courses depending on the nature of the study, the institution, and the access to medical personnel," she says. "There's not just one path, there are multiple morally acceptable trajectories for responding. But those need to be properly articulated both to the institution and to the human subjects."

Michael Hadskis, LLM, assistant professor of law at Dalhousie University, Halifax, Nova Scotia, has studied both the ethical and legal ramifications of incidental findings in MRI research.

He says an appropriate incidental findings management plan should start with the type of abnormalities likely to be uncovered during the study and which would prompt researchers to make a referral to a specialist.

"Some might be very minor, say non-acute sinusitis," he says. "Others might include an aneurysm ready to burst. The IRB needs to be very clear about what kinds of abnormalities will trigger a referral and when to refer."

A Stanford Working Group on Reporting Results of Genetic Research recognizes three categories of findings and makes recommendations for dealing with them. The highest, Category I, would include results that have "high clinical validity and utility," as well as "a high probability and magnitude of harm resulting from not offering the information," and for which "effective preventive measures exist."

The group recommended that those findings should be offered to participants, while findings that fall slightly below that level may or may not, depending upon the circumstances.

Hadskis says an IRB might take issue with the researcher's criteria for referrals.

"If the researcher says, 'We're not going to refer it unless it's an aneurysm that's just about to rupture,' the IRB might say there are less severe conditions that are still important and still might require a referral," he says.

Timing issues: In imaging research, the timing of a referral may be important, since a condition such as an aneurysm would require immediate action. In some cases, Hadskis says, a condition might be immediately apparent even during a screening, but in others, a problem may only show up with closer review days or weeks later.

"The researcher has to be clear as to when they are going to be looking for these issues," Hadskis says. "And when they spot it, how quickly are they going to get it to a radiologist, how quickly is the radiologist going to review it and have the situation addressed, or provide an opinion as to whether it needs more investigation.

"If there's going to be some time lag, let's hear about it."

The introduction of a specialist from outside the research team reviewing a subject's scan requires the express consent of the participant, Hadskis says. He says the researcher should ask for that permission in the initial informed consent, even though identifying information would be removed from a suspicious scan before it is shown to a specialist.

If the specialist who reviews the scan discovers that is it indeed a valid medical finding, or that follow-up steps need to be taken to determine if it is, then the researchers need to have a plan in place for how to communicate that to a

participant.

There are various means of doing so, all of which have advantages and disadvantages.

Because the finding is incidental to the study, the researcher is unlikely to be an expert in the subject's condition and may not be able to answer important questions about it. The researcher also may not have a long-standing relationship with the patient.

Hadskis says the specialist who confirmed the finding would be the most knowledgeable, but he says in his experience, some are not as good at communicating face-to-face with patients.

A family physician would have an existing relationship with the subject, but perhaps not the expertise to answer questions. In the case of either the specialist or family physician, the subject would have to give permission beforehand for research results to be shared.

"The IRB has to consider who's going to give this information, when and how, and in what context," he says. "It's very fact-specific. It will all depend on the circumstances."

On the other hand, **Susan M. Wolf**, JD, a professor of law, medicine and public policy at the Center for Bioethics, University of Minnesota, Minneapolis, recommends that results always be given directly to the subject by a member of the research team. She argues that the research participant alone should decide whom to tell about his or her findings.

When a finding suggests that there need to be further tests or scans, who should pay for them?

While it's not the responsibility of researchers to pay for extra testing, they should be ready to advise subjects who lack health insurance as to where they might go for help, Wolf says.

Informed consent: Hadskis says the entire pathway for handling incidental findings should be outlined in the informed consent document, so a participant knows exactly what would happen and who would be consulted if a finding turned up.

The consent should include the possible risks of an incidental finding (the physical risks of follow-up procedures, the psychological risks of learning about a potential problem, and the financial risks of learning about a serious ailment) as well as asking permission for any outside review of the subject's data. Doing this beforehand minimizes the stress a subject could encounter having to give permission at every step, Hadskis says.

"If you waited until there was something suspicious and then contacted the participant asking, do you consent to the [specialist] referral — now you're going to stress them out," he says.

Hadskis says outlining this process will inevitably add length to the consent document.

"My position is you don't need to scare them away — I'm happy for the language to be clear that it's a very remote possibility," Hadskis says. "But we have to inform them.

"Unfortunately, now your informed consent form is longer and, if not drafted properly, more complex. But it doesn't have to be particularly complex."

Wolf says that in the case of genetic or genomic research, the management plan also should include a process by which the researcher can talk to participants to see what kind of information they would want to be alerted about, and what they would rather not be told.

"In addition to educating research subjects about the possibility that incidental findings would be found, you should ask them for permission to seek a clinical consult because of HIPAA issues and also to get a sense of what kinds of information they want or don't want." ■

Give research results to study participants

Research shows participants want it

For years, the debate has continued about returning the results of research to the study participants who made it possible. Would such a process be expensive and unwieldy? Could it cause more harm than good, when participants receive bad news?

Many studies have looked at the attitudes of participants and investigators toward disclosing research results to participants.

Now researchers have looked at that body of research, to see what lessons it may hold for investigators and IRBs on this issue. What they found, says **David Shalowitz**, AB, a student at the University of Michigan Medical School, Ann Arbor, was strong support among participants for offering results, good or bad.

"I think the most surprising conclusion was that despite the fact that participants tend to have mixed psychological reactions to receiving research data, they overwhelmingly want to receive it," he says.

"I think one of the stumbling blocks for

investigators is a worry that they don't know how participants would react to receiving this kind of information — they don't want to do anything that would be taken the wrong way, that would be upsetting. But in the end, it looks like participants do want to at least get the chance to receive them if they want them."

IRBs should ask: Given that interest, he says IRBs should ask investigators upfront what they plan to do about offering research results when the study is completed.

"It shouldn't be an ad-hoc decision that's made later on down the road, when investigators discover that the results had meaning that they didn't think they would, or people were requesting their information and they hadn't planned for a procedure to deal with communication of the research results," Shalowitz says.

Shalowitz looked at 28 studies concerning communication of research results, some dating as far back as 1985.[1] The studies covered a range of different types of research, but more than half (16) dealt with cancer or genetics research.

In some, the results discussed were aggregate results, but others dealt with individual results, such as a person's individual risk for developing a disease. Eighteen studies asked whether participants wanted results (nine studies asked about aggregate results, eight about individual results, and one asked about both).

The median percentage of respondents who did wish to see results was 90%. "Given that, I think it's safe to say that probably everybody should get the offer," Shalowitz says.

Written results may suffice: His review of the studies found another interesting point — participants generally were open to the idea of receiving results in a written format.

This is important, Shalowitz says, because one stumbling block to returning research results has been the assumption that it would require costly and time-consuming personal interviews.

"It seems like participants are OK with receiving cost-effective methods — written communiqués, for example, newsletters, a phone call, the sort of methods that are not as cost- and time-intensive as, say, bringing in participants for a genetic counseling session," Shalowitz says.

"I don't want to say that there would never be a situation in which one-on-one counseling is necessary, but for the vast majority of studies, it seems that participants will accept a written communication of results with a phone number or some other means of contacting investigators if they have more questions."

Studies that looked at the impact of receiving results did report some negative reactions, including anxiety, anger, guilt, or upset, and beneficial reactions, including satisfaction and relief.

Shalowitz says the vast majority of participants believed it was important to receive the results, despite the potentially negative impact.

He says his study was limited by the lack of standardization in how the issue is researched. However, the studies done to date show IRBs should be discussing the possibility with researchers.

"There will be some expense, but that isn't really a good ethical argument against offering participants the opportunity to receive research results, unless investigators and IRBs decide that

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

- Evolving research: A strategy for enabling social-behavioral studies
- What to do when a subject wants to withdraw
- When is research payment an undue inducement?
- Here are some of the biggest challenges with accreditation

CNE/CME *questions*

5. Which of the following represents the best criteria for deciding whether a prospective study participant has the capacity to make an informed consent decision?
   A. Does the patient understand the risks and benefits of participating in research?
   B. Does the patient understand he has the option to not participate?
   C. Does the patient meet the legal definition of competency?
   D. Both A and B

6. Sen. Chuck Grassley (R-Iowa) has recently investigated payments drug companies made to psychiatrist/researchers, raising a national debate over researcher/clinician conflicts of interest. What is a solution Grassley proposes?
   A. Criminal penalties for physician/researchers who receive undisclosed incentives/payments from industry
   B. A requirement that IRBs vet all potential conflicts of interest on the part of researchers
   C. A national reporting system that would track payments made by the drug industry to researchers
   D. None of the above

7. Should participants in a study be given the opportunity to "opt out" of receiving incidental findings about potential individual health issues?
   A. Yes, always
   B. No, never
   C. Possibly, depending upon the type of study and other circumstances.

8. The researcher is usually the most knowledgeable person to explain the implications of an incidental finding to the subject.
   A. True
   B. False

Answers: 5. (d), 6. (c), 7. (c), 8. (b).

the offer itself would substantially compromise the feasibility of the research from the scientific perspective," Shalowitz says. "And I expect that that's going to be more of a rare circumstance than people fear it will be." ■

Reference

1. Shalowitz DI, Miller FG. Communicating the results of clinical research to participants: Attitudes, practices and future directions. *PLoS Med* 2008;5:e91.