IRB ADVISOR

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INSIDE

Clinical Trial Addresses the Tricky Process of Revealing Genetic Risk Factors for Alzheimer's

'In a way, we are giving these people a label they never had before'

By Gary Evans, Medical Writer

Cancer has been termed the emperor of maladies, but no illness carries quite the cruelty of Alzheimer's disease as it unwinds both memory and cognitive function. It may have been best described by Indian author, **Devdutt Pattanaik**: "Alzheimer's is the death of imagination."

Genetic research that could prevent or treat Alzheimer's — weapons to prolong a healthy mind — are under study. The caveat is that the human subjects recruited into trials must be willing to know if they carry the DNA markers that may predispose them to subsequent dementia. Is it better to know, while you still have your mind, that you may be at higher risk of losing it?

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The gene with the strongest influence on later Alzheimer's development is called ApoE4, explains **Jessica Langbaum**, PhD, associate director of the Alzheimer's Prevention Initiative (API) and principal scientist at Banner Alzheimer's Institute in Phoenix. The API Generation Study is enrolling more than 1,000 people who carry the most telling genetic signature for Alzheimer's onset, two copies of the ApoE4 gene. Under study are two experimental interventions, a

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CONTRIBUTING EDITOR: Melinda Young.
EDITOR: Jill Drachenberg, (404) 262-5508 (jdrachenberg@reliaslearning.com).
ASSOCIATE EDITOR: Dana Spector
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger.

EDITORIAL QUESTIONS
Questions or comments?
Call **Jill Drachenberg**,
(404) 262-5508.

vaccine and an inhibitor.

"The Alzheimer's Prevention Initiative is a multipartner, collaborative program that's doing clinical trials in people who, based on their age and genetics, are at highest risk of developing cognitive symptoms of Alzheimer's," she says. "The Generation Study, in partnership with Novartis and Amgen, is enrolling people who are at highest risk for the most common form of Alzheimer's in later life."

The Generation Study exists in two parts, and thus there are two consent forms.

"In the first part, individuals consent to receiving their genetic ApoE4 test results and to be followed for a one-year period to monitor the short-term and longer-term impact of receiving [those genetic results]," Langbaum says.

Individuals who are invited into the study may have zero, one, or two copies of the cognitive-disabling ApoE4 gene, with the risk of developing Alzheimer's ascending accordingly. The psychological effect of receiving this information, particularly for those at the highest risk with two copies of the gene, is addressed on initial consult and periodically thereafter.

"They meet with a genetic counselor or other healthcare professionals," Langbaum says. "They are told their ApoE4 results and are monitored over time. Those that have two copies of the ApoE4 gene, after they have been told their genetic information, are invited into the more traditional clinical trial phase to be randomized to receive either an active immunotherapy drug, a base inhibitor drug or matching placebo [for each arm of the study]. They will be followed up for up to eight years to see if treatment delays the onset of cognitive impairment or a diagnosis of dementia."

Follow-up

Whether they are in the randomized trial or not, all participants who agree to receive genetic test results are told those results in person by a genetic counselor and followed up by phone at regular intervals after that initial meeting.

"They receive a phone call soon thereafter within a two- to seven-day window," she says. "We check in on them as well as assess [any signs of] depression, anxiety, and other measures of psychological well-being. Then they are followed up six weeks thereafter, then six months and 12 months."

Langbaum and colleagues were careful to construct the IRB-approved trial in a way that participation does not reveal genetic status or risk factors for Alzheimer's.

"Recruitment in the study has to be done in such a way so that the invitation in and of itself does not disclose your ApoE4 results," she says. "In fact, we want people with a variety of ApoE4 results to come in because we really want to learn how receiving the genetic information is tolerated. Smaller studies have looked at this and said it is very safe and well tolerated to learn your ApoE4 test results. But most of those studies did not involve large numbers of people who are the highest risk — that is, they carry two copies of the ApoE4 gene. This study allows us to look at the impact of learning your genetic testing results if you have zero, one, or two copies."

Participants can enter the trial through GeneMatch, a web-based program and registry with partners

across the country. Those who enter the program through this method are provided a cheek swab kit to use at home. The swab is sent to an affiliated lab for DNA extraction and genetic testing. "Afterward, the DNA is destroyed and the results are kept in a safe and secure database," Langbaum says. "We have an algorithm that we run that invites selected individuals — we don't ever publicly disclose what that ratio is. It could be people with one, two, or zero copies of the ApoE4 gene. We invite them to participate in the Generation Study, but let them know that they have to be willing to learn their ApoE4 test results. The choice is always theirs whether they participate or not, and we also let them know that people with a variety of ApoE4 profiles are receiving this invitation."

If the gene match participants accept the study invitation, they are then passed along to the enrolling Generation site closest to them to sign a consent that they will receive their test results. Compared to past studies and general perceptions, Langbaum and colleagues have found the risk is relatively low, but development of subsequent Alzheimer's cannot be ruled in or out regardless of the genetic results.

"We worked with an epidemiologist to analyze data from several different cohort studies to be able to tell participants information about their risk of developing Alzheimer's dementia by age 85," she says. "[We found] if you have two copies of the ApoE4 gene, then the risk ranges from 30% to 50% of developing Alzheimer's dementia by age 85. We also acknowledge that there are factors that can either increase your risk or decrease your risk — things like family history, a history of heart disease. For the most part, our initial people are coming back and saying, 'Wow, that's much lower than I thought it was.' But we can't give a very accurate [estimate]. We can't say to this individual, 'Your risk is 47%.' We are not there yet.'"

The purpose of the study is to test whether two investigational drugs called CAD106 immunotherapy and CNP520, administered separately, can slow down the onset and progression of clinical symptoms associated with Alzheimer's in participants at the risk to develop clinical symptoms based on their age (60-75 years) and genotype. Both drugs target amyloid plaque in the brain, a biomarker for increased risk of dementia.

"OTHERS SAY THEY ARE NOT INTERESTED BECAUSE THEY ARE AFRAID OF THE UNINTENDED CONSEQUENCES WHEN IT COMES TO THEIR MEDICAL AND LONG-TERM CARE INSURANCE."

Implications for Other Research

The study owes a debt to prior oncology research, and holds the promise to repay that to other areas of research that reach such an ethical impasse.

"It is a model not only for Alzheimer's disease, but for other neurodegenerative diseases and other disease areas," Langbaum says. "For example, oncology has made a great deal of progress at disclosing genetic results. In fact, in our model for genetic testing and disclosures, we have really learned a lot from our colleagues in oncology. As we move into this, we are telling healthy people their genetic risk and trying to see if we can prevent the onset of cognitive impairments."

In that sense, this line of research is nearing the edge of the known map in terms of genetic disclosures in clinical trials.

"In a way, we are giving these people a label that they never had before," she says. "This is an important new space that we are in of research. How do we continue to monitor the well-being of these individuals and what protections are available for these people?"

For instance, the Genetic Information Nondiscrimination Act (GINA) of 2008 doesn't clearly cover this situation, she says.

"There are many caveats to [genetic test disclosure] — long-term care insurance and things like that," she says. "We have to make people aware of all these factors before we disclose. This is uncharted territory from a federal protections standpoint."

The trial requires agreement of disclosure of results to participate, but some people don't want to know for their own reasons, or because it may end on up their medical records as a pre-existing condition.

"Most people say they may get their life insurance in place beforehand," she says. "Others say they are not interested because they are afraid of the unintended consequences when it comes to their medical and long-term care insurance." ■

Research on Brain Scan Risk of Alzheimer's an Ethical Challenge

Informed consent, disclosure despite lack of treatment options

While different than genetic signs for dementia, biomarker information found in research brain scans also can suggest heightened risk for developing Alzheimer's disease, and thus the disclosure or withholding of results raises ethical questions for IRBs and investigators.

In particular, PET scans show levels of amyloid plaque accumulation within the brain, which may signal an increased risk of developing full-blown Alzheimer's, particularly in patients who already have dementia symptoms. The clinical options and interventions are limited, and thus PET scans are not typically covered for reimbursement.

"[PET scan results] are not medically and clinically actionable in the traditional sense of that term," says **Jennifer Lingler**, PhD, who studies ethical issues in dementia care and research as an associate professor of Health and Community Systems at the University of Pittsburgh. "But one of the things that makes this an interesting area of research is that these scans are being utilized with really increasing frequency in all sorts of studies of cognitive aging, from looking at normal, cognitively healthy older adults to people with all different forms of dementia. These scans are becoming a gold standard of sorts for identifying whether there is Alzheimer's pathology in the brain."

Thus, in research studies that include PET scans, investigators and IRBs must decide whether and how to present such information, for which there is little medical recourse but could be psychologically devastating to research subjects.

"If you see a tumor on a brain scan, you have a different set of obligations to a patient and possibly extending that communication to their clinical providers," Lingler says. "If there is not a treatment that can be implemented, it really falls into more of a gray zone ethically. There is some uncertainty for investigators: 'Do I have an obligation to even share this information with my participants, let alone ask them to consider relaying this back to their medical providers?'"

Lingler and colleagues designed a study[1] to assess disclosure of amyloid scan results to people with mild cognitive impairment (MCI). They wanted to ensure comprehension of the scans and any subsequent results by developing educational materials for use in pre-test counseling and post-test disclosures. The research subjects had MCI, but were participating in a simulated script that modeled the experience of having a brain scan and being told the results. The participants received fictitious but realistic information regarding brain amyloid status, followed by an explanation of how results affect Alzheimer's disease risk. The study and analysis supported the following recommendations:

- offer pre-test counseling,
- use clear graphics,
- review participants' own brain images during disclosures,
- offer take-home materials, and
- call participants post-disclosure to address emerging questions.

Lingler and colleagues concluded that the research participants understood the limitations of amyloid imaging, but nevertheless viewed the prospect of learning one's amyloid status as valuable and empowering. Finding this approach promising, the researchers are now working on a study using actual brain scans and real results that may be shared with people with MCI. *IRB Advisor* asked Lingler to provide a few more details about this emerging line of research.

IRB: What are some of the basic implications of your research for IRBs and investigators?

Lingler: I think investigators that are considering releasing these results to research participants should offer pre-test counseling of some sort. They would have an obligation, as this point in time, because we don't know what the psychological repercussions might be. There [needs to] be some follow-up monitoring and have safeguards in place for [recognizing] any adverse psychological outcomes, and a plan in place for addressing those. We would also have to, of course, recommend at this point in time that individuals be screened in advance for any mood instabilities, suicidal ideations, or things of that nature. We don't want to be overly paternalistic, but investigators should take those things into account.

For IRBs, my suggestion would be to evaluate for the potential risk of the scan itself distinct from a set of risks of receiving the results. They need to add a second layer to this instead of just the traditional mindset of looking at the safety profile of things like the imaging agent or the PET scan itself. There is a second layer now associated with the risks of disclosing and withholding

that information. So IRBs need to think about balancing a participant's right to their own research data versus the psychological risks that [disclosing the data] might present.

IRB: So the pre- and post-counseling about the procedure and disclosure of results all fall under aspects of informed consent?

Lingler: Our current study is finding that the counseling session is longer and more detailed than the typical informed consent process. The informed consent process [typically] zeroes in on more consenting to the research study, and as part of this research a scan is going to be done. Really, people have to consent to the physical risk of the scan. The idea of whether they want to know the scan results is sort of a second layer, and we haven't found it very efficient to try to roll all of that into informed consent. Even if we view informed consent as a process, a dialogue, an exchange, the type of counseling that we are suggesting, promoting, and using in our current study is more detailed and more of a separate issue for people to think about. Because we also would not want to exclude people from studies just because they don't want these results back. There are plenty of studies where, for scientific purposes, they do these scans and there wouldn't be any reason to limit those participants who, in fact, don't want to have the results.

IRB: Just to clarify — regarding the simulated sessions in the published study, this was a scripted interaction with people with MCI that did not involve assessment or disclosure of the research participant's actual medical data?

Lingler: Exactly. In the simulated sessions, we recruited people and told them we are trying to develop and refine patient education materials so we will know how well our [approach] works. We were looking for people to listen and view the information we were developing. In the simulation, we asked people to imagine that they had undergone a special type of brain scan. There was a script that was administered, and the individual also had a copy of the script in hand because they do have mild cognitive impairment. It was scripted and one of the main reasons for that was to ensure that, for research purposes, everyone is getting the exact same [message]. We wanted to evaluate how much they understood — and, obviously, that could be compromised if different people hear different things. We told them at the outset that this is the script you are going to hear, but the results were fictitious.

IRB: Even though there is little that can be done in terms of treatment, are you finding that participants still want to know their brain scan data and, to some degree, their Alzheimer's risk? Does it allow them to make life decisions or have some clarity about their mental health?

Lingler: They need to think about whether this is information that they want to have. As we reported in the article and in our current study, whether we are doing simulations or doing the real thing, we have seen the gamut of every type of preference you can imagine. We've seen families that want the results but the patients don't, and vice versa. People who don't want the information versus people who do want the information. In our current study, because people have the opportunity to get these results, we are seeing a select population in a sense that is very information-seeking. We ask them at the time of study entry, before they undergo the pre-test counseling, "at this point in time, about how interested are you in receiving your results on a 1 to 10 scale?" And the average is over 9. People are highly interested, and the families are averaging between 8 and 9 in terms of their interest in getting the results. Most are participating in the study because they want the results. People are very interested and they know they can't get this scan in clinical practice. There is not reimbursement for it by CMS.

But our job is to work with them and make sure they really understand the limitations of this and they don't overestimate and equate a scan diagnosis with Alzheimer's. They also understand that a negative scan does not mean they are never going to get dementia syndrome of any sort. So, the population we are working with has mild cognitive impairment. People with full-blown Alzheimer's — if they have a positive scan, in a clinical context it's not much of a game-changer. It's just confirmatory at that point because they already have the disease.

Interesting and potentially valuable is this subset of people that we have been focused on with mild cognitive impairment. We know they are exhibiting cognitive changes and they are at high risk for developing Alzheimer's disease. In this population, the amyloid plaque scan can really help to distinguish those whose syndrome of MCI is likely to represent an ensuing Alzheimer's process versus people who might have an MCI for other reasons and may not be on an Alzheimer's trajectory. Although there is not a medication we can put them on, for personal [reasons] it might be valuable for them to understand. ■

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Meeting Management ABCs From an Expert IRB Chair

Know your members' expertise, pet peeves

After 32 years as an IRB member and 20 years as chair, one IRB expert says the key to IRB meeting success could be boiled down to one word: Respect.

"Be respectful," says **Peter Iafrate**, PharmD, chair of the University of Florida IRB in Gainesville. Iafrate spoke about IRB chair meeting management at PRIM&R's 2016 Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA.

"It works both ways," he says. "We expect investigators to respect the process of human subjects review, and board members need to respect that these people are trying to do good research."

Iafrate should know. He estimates he has chaired around 750 board meetings. Also, for the first 2.5 decades that he was on an IRB, he also was the institutional director of pharmacy. In more recent years, he has been an IRB chair as a full-time job.

"I do more than run the board meetings," Iafrate says. "I help oversee the office."

Iafrate has the following best practice suggestions for running a better IRB meeting:

• **Know thyself.** "If you are going to run an IRB, then you have to know first who is your IRB, what is the membership?" Iafrate says. "Ideally, you have both new members and veteran members because it's important to get different perspectives."

The board also needs regulatory and institutional knowledge.

"For example, our board of 22 members has only four people who have been on the board for more than 15 years," Iafrate says. "About 60% of the members have been on the board for less than two years."

But having even a handful of experienced members is important. It's also important to have professional diversity. The University of Florida IRB has members from the colleges of medicine, dentistry, pharmacy, nursing, allied health, and other areas, he says.

"Make sure your members represent the types of protocols you typically see," Iafrate says.

• **Share the workload.** "Most IRBs have a designated reviewer system," he says. "We have a designated reviewer system with a lead reviewer and two secondary reviewers."

All board members receive information electronically, and the designated reviewers also bring up particular issues.

• **Give advance warning.** IRB members shouldn't go to a board meeting without knowing in advance which issues might be controversial, Iafrate says.

The chair can look through the agenda for something that might require longer discussion. Then the chair could give board members a heads-up on the item.

For example, Iafrate might tell the board that a particular study plans to enroll wards of the state, which is a major issue related to enrolling a vulnerable population.

"The other thing I would do is if I have a controversial issue that might require some kind of outside help, like legal services or a privacy office, I'll make sure someone from that office is there for that discussion," he says.

• **Provide comfortable space.** When IRBs meet for hours at a time, it's important to have a comfortable meeting space. There might be a kitchen area near the conference room. Chairs should be comfortable. Perhaps there are microphones at each seat. If the meeting is early morning, then breakfast could be provided. Likewise, if the meeting stretches past noon, there could be lunch.

"Members should feel free to move around, to step out of the room," Iafrate notes.

• **Open meetings.** While some institutions do not permit researchers and research staff to attend the IRB meetings, they are welcome to the University of Florida IRB's meetings, Iafrate says.

For one thing, the IRB has no choice since it's located in a state with a sunshine law that requires any state meeting to be open to the public. This rule applies to university meetings as they are public institutions, he explains.

But the IRB also encourages researcher attendance because it can help streamline the review process. "If the principal investigator is there to answer questions, the likelihood of the study getting tabled goes down significantly," Iafrate says. "So for us, it's helpful."

This doesn't mean the IRB allows the investigator to dominate the meeting, however.

"As chair, you have to run the

meeting," Iafrate says.

• **Control air traffic.** "One thing you have to do as a board chair is a little bit like air traffic control," Iafrate says. "There are a lot of things going on that you have to pay attention to: your time, who is in the room, whether you can sense someone getting agitated."

Chairs must pay close attention to the room's atmosphere, review the long list of items on the agenda, and always think about what's coming up next, he suggests.

When a board member is filibustering, talking for well past their allotted time, it's a good idea to keep the discussion going with a well-timed interjection. "I think the best way to do it is to inject some humor into it," Iafrate says.

"So if I have a member going on and on about a particular protocol, I could say something like, 'Chuck, you know they served lunch a half hour ago, and I think everyone is getting hungry,'" he says.

The other strategy is to appeal to the length of the meeting: "Look at the clock and say, 'We've got 30 more things. Is there any way you could summarize where you're at with this?'" Iafrate says.

• **Give occasional overviews.** After several people have spoken on a topic, it's a good idea to provide the board with an overview of the discussion.

"I'll be busy jotting down notes, and then sometimes I'll cut off the discussion by saying, 'Okay, what we have so far is this, this, this, and this. Is there anything new that anybody has?'" Iafrate says. "Or I can say, 'It seems like we're circling the airport at this point. Does anybody have anything additional they want to say?'"

It's a fine line between allowing people to talk freely and cutting them off prematurely, he says.

• **Work with PIs.** Investigators attending the meeting might receive a handout that explains what is happening. Guests, including principal investigators, sit in chairs off to the side of the U-shaped board table. The board discusses the study first and, when it's appropriate, Iafrate will call on the study's representative.

"Sometimes they want to jump into the conversation right away, and I'll say nicely, 'I'll tell you what, let the members get all of the issues out, and then I'll let you talk,'" Iafrate says.

It's the chair's role to manage those kinds of details, such as when the study representatives speak, how the board is perceived by guests, and how the interaction goes.

"We're all in it for the same purpose, but sometimes the board can sound a little harsh and I have to pay attention to that and try to soften the discussion without softening the issue," he explains.

"When the discussion is over, I'll ask the study staff to leave the room and I'll say something like, 'If we could get you to step out for a few minutes, we'll come out and let you know the board's decision,'" Iafrate says. "Then I'll thank the visitor for helping us inform the board's discussions."

• **Tone down attitude.** Occasionally, there is a board member whose tone sounds harsh and overly critical. The IRB might receive complaints from meeting visitors. When that happens, Iafrate might have a meeting with the board member to discuss how she or he is coming across.

"I want to make sure they are aware they're coming off a little too aggressive or harsh," he says. "But at some point that might just be who they are, and if they don't want to change, I'll dismiss them from the board."

• **Deliver gentle reproach.** IRBs often receive submissions that are poorly prepared or are lacking in necessary information. When this happens, the board will need to let a researcher know that the submission needs work, but this can be done diplomatically.

Iafrate offers the following examples of the wrong way and the right way to deliver criticism:

- Wrong way: "You obviously did not think through this protocol before you submitted it."

- Right way: "There are a lot of issues you didn't address. Would you like someone to contact you about helping with this submission?"

• **Predict pet peeves.** With experience, IRB chairs can predict each board member's pet peeve. "It might be someone who is always looking at the benefit section of a consent form to make sure it's fairly described," Iafrate says.

• **Make voting confidential.** "One thing that has changed for our board is we used to vote by raising your hand, and now we have a simple system that uses an electronic vote," Iafrate says. "There's a dynamic to voting by hand: Everyone knows how you voted."

This can lead to people voting with the majority out of peer pressure, not because they truly feel that way about the study.

The new electronic system has a keypad for each board member. They can type in the number one for "yes," the number two for "no," and the number three for "abstain."

When the chair calls for a vote, the projection screen shows the tally, and when it's done confidentially through the electronic system, the vote almost never is unanimous. People feel more at liberty to vote as they like, rather than voting one way out of peer pressure.

• **Provide follow-up.** Once the meeting is over, the chair's job is not done. Now the chair has to make sure that the board's decisions are commu-

nicated to all stakeholders, Iafrate says.

"I know that at the end of the meeting I'm going to hear from certain investigators, and I'll prepare for that," he says.

"Also, I make notes during the meeting about the issues we'll need to follow up on," Iafrate says. "It might be to tweak this rule or get this issue out to the research community because a lot of people are doing this wrong." ■

When it was Time to Standardize, IRB Went With a P&G Committee

Collaboration and consolidation of IRBs likely will be an ongoing trend that necessitates action to reduce problems and improve streamlining — in other words, best practices.

IRBMED, the IRB office at the University of Michigan Medical School in Ann Arbor, decided the best practice would be to develop a practice and guidance (P&G) committee to document IRB standard procedures and pilot projects.

"There was an effort to work on developing and standardizing some best practices, but there needed to be a formal structure that could support that ongoing development and dissemination of best practices," says **Judith Birk**, JD, IRBMED director.

"This was an opportunity to bring it under the direction of a consistent group that we could all evaluate and finalize, and then disseminate the best practices," Birk explains. "It was just an opportunity to take an action that was started previously and give it consistency."

The committee also is an opportunity to bring together the regulatory staff and go over regulatory rules, standardizing practices across the boards, says **S. Joseph Austin**, JD, assistant director for regulatory operations at the University of Michigan Medical School.

The P&G committee, which Austin attends, meets once a week for one hour. "We have five three-person teams in the office to support the boards and perform the regulatory reviews for applications coming in, and for the P&G committee we have representatives from each of those teams," Austin says.

"We pull in additional individuals for their expertise," Austin says. "P&G is six to eight people."

The committee serves as a working group. It creates three different types of documents, including the following:

- a P&G internal document that is instructive on how to do something standard within the office,
- a companion, procedurally oriented piece that delves deeper into the procedures and explains how to work within the electronic application, and
- a statement of practice, a document that alerts the research community about what the IRB's practices are, including explaining flexibility initiatives and when these will be used.

Typically, someone on the committee will create a draft document, including flexibility initiatives.

"It's the practice across the country to take advantage of flexibility in the regulations, based on how each institution has chosen to set their FWA after they unchecked the box," Birk says.

Birk refers to the Federalwide Assurance (FWA) for the Protection of Human Subjects and the growing trend of institutions, like the University of Michigan, "unchecking the box" to allow for more flexibility in federal oversight. What it means is the institution no longer voluntarily applies the Common Rule federal regulations (45CFR46) to all research.

"Institutions that uncheck the box are permitted to develop equivalent protections that may differ from the Common Rule," Birk explains. "To do so, you can reduce regulatory burden by still offering appropriate protections for human subjects; for example, you can extend the IRB approval beyond one year to two or more years for low-risk studies."

The P&G committee created the document about flexibility to indicate its procedures for flexibility initiatives, she adds.

Before each P&G committee meeting, members receive materials to review. They're expected to arrive at the meeting with ideas and suggestions.

"That helps us have productive meetings and move these documents along," Austin says.

The committee discusses the suggestions and reaches a resolution on what should be done. Then it's written into a document that will be further vetted at a group meeting. After the committee decides on the document, it might be vetted to other institutional leadership offices and individuals.

"If it's something that we need the general counsel to weigh in on, it will go there," Austin says. "If it's just about workflow or general practices, then it will stay within the office."

Members of the P&G committee, other than core administrative members, are rotated annually, Birk says.

Also, the committee's task list

is kept fluid so it can be modified quickly to adapt to any emerging office needs, Birk says.

"Several times a year, we use that committee to help us with priority issues to develop and write our guidance," she says.

The guidance documents are discussed at weekly staff meetings. As people use them, they may offer suggestions or ask for a clarification, Birk says.

"It's not uncommon for one of our staff members, during a discussion, to actually refer to a practice and guidance document or to ask if they can develop what we're discussing," Austin says.

"They're also very beneficial to new staff joining the office," he says. "If they don't know our internal practices, there now are outlines for how to do it and they can reference them."

The P&G committee's guidance fills a big gap for the IRB, Birk notes. "Before, we didn't have a process that tied together all the guidance out there or that gave us a portal to develop new guidance; it really met an unmet need." ■

IRB Designs Process to Separate QI from HSR

The most commonly asked question of the Intermountain Healthcare IRB in Salt Lake City has been: "Is this quality improvement or is it research?"

That question is very important to the IRB because it's important for researchers to better understand regulatory definitions, says **Shelby Moench**, CIP, IRB administrator at Intermountain Healthcare.

"What we're trying to point out is that sometimes QI projects can meet the definition of research," Moench says.

The IRB has an online determination form that provides definitions and asks basic questions to help investigators and the IRB decide which are research and which are quality improvement. The four-page form, for instance, defines research as "a systematic investigation including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

The determination form also includes the following questions:

• **Section 1:** Describe the target population. Who (or whose information) does the project include (employees, physicians, patients, etc.)?

• **Section 2:** Is your project a systematic investigation?

- Is this project (or activity) being designed and implemented for internal Intermountain Healthcare purposes (in other words, the information gained from this project is intended to be used within Intermountain Healthcare)?

- Does this project consist of operational activities?

- Does this project aim to expand the knowledge of scientific discipline or scholarly field?

• **Section 3:** Does this project involve human subjects?

A human subject is a living individual about whom an investigator (whether professional or student) conducting research obtains:

1) data through intervention or interaction with the individual, or

2) identifiable private information.

- Will you gather data about living individuals through intervention or interaction?

- Will you gather data about living individuals that is private?

- Will you gather identifiable data about living individuals, or is the individual's identity already known or can be ascertained by the investigator?

- **Data Collection Methods:**

Describe the methods to be used to gather data:

- interviews,
- survey,
- medical record review,
- other.

If conducting a medical record review:

- Describe the data you will review and collect (name dataset or database from where data will be abstracted, list the data elements, etc.).

- How was data originally gathered (from an existing IRB-approved protocol, a clinical data base, QA/QI database, etc.)?

- How will the data be analyzed?

- Who will analyze the data?

- Where will the dataset be stored?

- Will data be shared outside of Intermountain Healthcare?

- Can data be directly or indirectly (by code) linked to an individual?

- **Conditions for determining status:**

- Do you have any plans to supplement or modify quality improvement data?

- Do you have plans to make the data generalizable outside of Intermountain Healthcare?

- Do you plan to use the data to expand the knowledge base of a scientific discipline?

- Is the student project being conducted (in part or in full) to meet the requirements of a university-level degree program?

- Does the project assign participants to different treatment groups or arms?

- Does the project include a control

group? In other words, will the project withhold a normally received intervention or treatment from some or all participants?

- Will individuals involved in the project be exposed to risks or burdens that would not be encountered otherwise? Consider physical, psychological, social, or economic factors.

- Will the project collect and record identifiers and/or personal health information (PHI) for purposes other than treatment, payment, or operations at Intermountain Healthcare?

- Is your project federally funded?

- Does your project include an FDA-regulated product?

The goal in educating researchers is to both publish educational materials, like the determination form, but also to educate investigators through one-on-one discussions about their projects, Moench says.

For instance, in one recent conversation, Moench met with an instructor who wanted to improve the process for educating employees and improve science by showing that her method of education was valid.

"I would say, no, that she didn't know it was research because the project she described was in a gray area, and maybe it could be a quality improvement project," Moench recalls. "These are not black-and-white decisions, and it's not always easy to make a call."

At Intermountain Healthcare, the IRB has the final say on whether a project is human subjects research or a quality improvement project. If the IRB calls a project research, then the researcher has to submit it for review or risk being out of compliance, she says.

"We're hoping to get to the point where there's an automatic form that tells people, 'No, thanks, you don't have to submit,'" Moench says. "But we don't have the questions refined that way yet, so the form goes to my team for review." ■

People with Mental Illness Often Excluded from Clinical Trials

If a medication for major depression has a dangerous adverse interaction with a different medication that's being studied in a clinical trial, will it be discovered by researchers and reported in the literature? Not likely, if no one enrolled in the study has major depression.

"We need to make sure that the people we study are like the people we treat," says **Keith Humphreys**, PhD, a professor of psychiatry and behavioral sciences at Stanford University. "The healthcare system takes care of many people with psychiatric disorders all over the system, not just in psychiatry."

Previous research has shown that women and older people are often disproportionately excluded from research. "We wanted to see if the same was true of people with mental illness. It's an important question to ask because people with mental illness are just as likely, or even more likely, as the general population to have serious medical problems," says Humphreys.

The researchers found that half of 400 highly cited randomized trials across 20 common chronic disorders reported possible or definite psychiatric exclusion criteria.[1] Negative attitudes about people with mental illness are one likely reason, researchers found. Another is that researchers make blanket assumptions about lack capacity to give consent.

"The problem is that research then doesn't generalize as well to people with psychiatric problems as it does to the rest of the population," says Humphreys, the study's lead author.

When enrolling patients with psychiatric disorders in research, it's ethically important to "balance research opportunities with research protection," says **Cynthia M.A. Geppert**, MD, MPH, chief ethics consultant at New Mexico Veterans Affairs Health Care System in Albuquerque.

"In areas where psychiatric patients may have vulnerabilities such as impairments in executive functioning, efforts should be made to minimize risks and maximize the benefits of participation," Geppert says.

Previous research indicates that patients with serious mental illness want the opportunity to express their altruism and autonomy through research participation.[2] "These patients should be not prevented from enrolling in research based on misconceptions about capacity," says Geppert.

The presumption that many psychiatric patients are incapable of providing informed consent for research is still prevalent. "This is despite empirical work demonstrating that the majority of patients are able to provide informed consent for research participation," Geppert says. For the small number of psychiatric patients who lack the capacity to consent, she suggests that proxy decision-making can safeguard patients' welfare while permitting participation.

Marilyn A. Fisher, MD, MSBio-

ethics, associate professor at the Center for Biomedical Ethics Education & Research at Albany (NY) Medical College, says, "Because patients who are decisionally incapacitated may seem to be convenient, gullible, and exploitable research participants, they have the right to be afforded extra protections from the dangers of participating in research." The following are two primary ethical concerns:

• People with psychiatric conditions are particularly vulnerable to coercion.

Coercion may cause an institutionalized person to consent to participate in a research study for reasons other than wanting to contribute to scientific knowledge to help others, due to fear of retribution, says Fisher.

"In order to minimize effects of coercion, the potential study subject should clearly understand that participation will not be rewarded and nonparticipation will not be punished," says Fisher.

Barton W. Palmer, PhD, professor of psychiatry at University of California, San Diego, notes that a cornerstone of ethical research is that it be voluntary. This means participants cannot be coerced or unduly influenced.

"This can raise complex issues when the investigator also wears the hat of clinical provider, and is recruiting his or her own clinical patients into a protocol," says Palmer. While this is not necessarily unethical, the potential for undue influence needs to be carefully considered, he says.

• People with psychiatric conditions may have a permanent, or fluctuating, lack of capacity.

"The informed consent process should be carried out in a way that is understandable to the potential research subject, and at a time when he or she has the most capacity for understanding the information discussed," Fisher says.

Upon diagnosis of a psychiatric illness, during a period of lucidity, advance directives can be sought for eventual participation in the research study, suggests Fisher. "The patient should have the opportunity to contemplate the study over a period of time, to ask questions about the study, and to discuss it with his or her support people," says Fisher.

To declare all patients who are decisionally incapacitated ineligible to participate in clinical trials violates the ethical principle of justice, says Fisher. "This is because other diseases are having active research performed in hopes of finding their cures, so cures should also be actively being sought for psychiatric disease," she says.

Certain psychiatric disorders are associated with greater risk of impaired decisional capacity. However, says Palmer, "a large body of research has shown that there is considerable within-group heterogeneity — such that it would be inappropriate to equate a psychiatric diagnosis with impaired capacity."

Another challenge is that the participant has be be able to follow the study processes — taking medications as scheduled, avoiding anything contraindicated, completing visits and procedures as scheduled especially for safety assessment — throughout the entire study.

Moreover, it is not a person's general decisional capacity that is at issue — rather, the capacity to make a very specific decision. "A person may retain capacity to make a decision about a straightforward protocol with a good risk/benefit ratio, but have questionable capacity to decide in regard to a more procedurally complex protocol, or one in which the risk/benefit considerations are more complicated," says Palmer. Therefore, capacity must be evaluated on a situation-specific basis, he says.

"It is important to consider that the comprehension of a potential participant is influenced not only by his or her decisional capacity, but also by the quality of the consent process," adds Palmer.

Except perhaps with very high-functioning individuals, it is generally inappropriate to simply have the person read and sign the consent form. "Rather, consent should be conducted as an interactive process," says Palmer. This includes checking of participant comprehension with open-ended questions, provision of corrective feedback, and further assessment of comprehension.

"When decisional capacity is in question, formal assessment with an established tool should be considered," Palmer adds. ■

REFERENCES

1. Humphreys K, Blodgett JC, Roberts LW. The exclusion of people with psychiatric disorders from medical research. *J Psychiatr Res* 2015; 70:28-32.
2. Roberts LW, Warner TD, Brody JL. Perspectives of patients with schizophrenia and psychiatrists regarding ethically important aspects of research participation. *Am J Psychiatry* 2000; 157(1):67-74.

COMING IN FUTURE MONTHS

- Expand view of vulnerable people
- Try this strategy to better monitor noncompliance
- Common Rule changes
- Teach student scientists better practices

IRB ADVISOR

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to AHCMedia.com, then select My Account to take a post-test.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE QUESTIONS

1. A genetic study of Alzheimer's treatments found people with two copies of the ApoE4 gene have what risk of developing the disease by age 85?

A. 30% to 50%
B. 55% to 75%
C. 25%
D. 80% to 90%

2. A study assessing disclosure of brain scans to amyloid imaging recruited which type of research participants?

A. Those with full-blown Alzheimer's.
B. Healthy subjects over 65 years.
C. Those with mild cognitive impairment.
D. All of the above.

3. Which of the following is not a good strategy for managing an IRB meeting, according to Peter Iafrate, PharmD?

A. Give IRB members advance warning of any controversial items on the agenda.
B. Hand out a list of protocols on the agenda along with the staff's recommendation for whether to approve or not approve each one.
C. Provide a comfortable meeting space.
D. Guide IRB members into less abrasive ways of discussing protocols.

4. What does it mean to "uncheck the box" on Federalwide Assurance (FWA) for the Protection of Human Subjects?

A. The IRB decides to not accept international studies.
B. The institution is not accepting federal funding for research.
C. The institution is no longer voluntarily applying the Common Rule federal regulations to all research.
D. All of the above.

CME/CE OBJECTIVES

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

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