IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

2003 Salary Survey Results inside

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Behavioral research risks may not be life or death, but subjects could suffer

Think outside of biomedical box when assessing risks

IRB members who are accustomed to dealing with the serious potential physical risks associated with many biomedical research projects may give little thought to the risks inherent in social-behavioral research.

But this attitude is a mistake, according to two social-behavioral research experts, who are scheduled to speak at the Contemporary Issues in Human Research Protections conference on Nov. 17 at the Iowa Methodist Medical Center in Des Moines.

IRBs that deal primarily with medical research sometimes lack an appreciation for the risk possibilities in social-behavioral research projects, notes **Brenda Ruotolo**, CIP, team manager for one of the institutional review boards at the Columbia University Health Sciences in New York City.

"It's obvious when you're administering an investigational drug that you are doing research," Ruotolo says. "You have a new drug and are testing it for safety and efficacy, often collecting quantifiable data."

In social-behavioral research, the methodology and data collection may be very different, she adds. "However, subjects deserve the same protections, and IRBs need to know how to apply the same review criteria."

Also, biomedical IRBs may focus on physical risks and overlook the range of risks that includes social, economical, financial, and psychological, Ruotolo reports.

Some researchers and IRB members erroneously believe that the federal regulations for protection of human subjects do not apply to social-behavioral research, says **George Pospisil**, MA, CIP, public health analyst for the division of education and development at the Office for Human Research Protections in Rockville, MD, which is cosponsoring the meeting.

However, it's a myth to think the federal regulations did not include social-behavioral research because the documents that preceded the regulations definitely had behavioral and social research in mind, Pospisil says.

Historical examples of research abuses include social-behavioral studies: for example, one study about stuttering, he notes.

"There was a study about stuttering involving young people, some who stuttered and some who did not stutter but were induced to stutter," Pospisil says. "Some of those people who did not stutter before the study continued to stutter the rest of their lives and suffered emotional and personal consequences of that."

Decades later, some of the families of those research subjects are bringing litigation against the research institution, he adds.

Other examples of social-behavioral research that had greater than minimal risk included a study in which research subjects were asked to play the role of guards or prisoners in a mock prison.

"The study was forced to be terminated in the middle of the study because of the emotional damage done to some subjects," Pospisil recalls.

Another classic example is a study in which subjects were placed at a console and told they had control over giving electrical stimulation to another person, he says.

"They were led into a situation in which they thought they were delivering lethal levels of electricity to another person to kill them; and because of the guilty feelings and embarrassment they felt, some of those people have needed psychological help," Pospisil says.

"Those are just some examples that illustrate that social-behavioral research risks can be more than minimal, and that psychological risks are real risks," he adds.

In more recent times, the risk of disclosure of private health or personal information can create a significant risk to some research subjects.

"If you're doing a survey over the telephone, depending on the nature of the questions and focus of the study, there can be some information that's collected that could put the respondent at risk if that information was disclosed," Ruotolo says. "And yet it can be routine in a protocol that involves a telephone interview to request a waiver of consent."

Privacy increasingly is an important risk consideration as researchers make greater use of the Internet for surveying subjects and visiting chat rooms, Pospisil says.

Concerns about privacy and other risks pertinent to social-behavioral research have led to the creation of the Social Behavioral Research Working Group of the National Human Research Protection Advisory Committee, Pospisil says.

The working group has been developing a set of principles that would apply more specifically to behavioral research, he adds.

"Quite frankly, in cases of behavioral research most of the activities involve minimal risk, and there is flexibility built into the regulations," Pospisil says. "So that even if an IRB is reviewing the research, the flexibility allows the work to be

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Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262- 5483, (lee.landenberger @thomson.com).
Managing Editor: **Alison Allen**, (404) 262-5431, (alison.allen@thomson.com).
Production Editor: **Nancy McCreary**.

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Editorial Questions

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reviewed a little faster and with fewer restrictions being applied."

IRBs that deal with social-behavioral research can make good use of exemptions, waivers, and expedited review procedures, Pospisil advises.

However, IRBs should keep in mind that sometimes when investigators submit a proposal for exempt research they may not include pertinent information that would help the IRB determine whether the proposal truly does pose minimal risk, Ruotolo says.

"They may not make it clear whether they are collecting identifiers," she adds.

A solution would be for IRBs to require investigators to list all of the necessary information and to make it clear that if investigators leave out pertinent information about the study then it will take the IRB longer to review the proposal, Ruotolo states.

"The focus comes down to the IRB to have clear policies, and these need to be communicated to investigators and staff," she says.

"If an institution has a social-behavioral research board, then that's great. But if one IRB is reviewing both biomedical and social-behavioral research, then the board needs to be well educated and have members with appropriate expertise," Ruotolo advises.

If it's really research

IRBs and institutions need to avoid both treating social-behavioral research the same way they would treat biomedical research, and they need to avoid the other extreme of ignoring it altogether, Ruotolo and Pospisil say.

"I see two practices out there in the field that are the extremes away from the actual definition [of human subjects research] itself," Pospisil says. "Sometimes IRBs are very zealous in application of the regulations and want to extend the jurisdiction of regulations to activities that may not be research."

In these cases, OHRP officials will try to let IRBs know that they don't need to call every classroom exercise, for example, research unless it is conducted in the outside world or the institution's own policies require them to review such protocols.

"The IRB has to know the regulations, and the institution has to have firm policies on how they are applying the regulations," Ruotolo says.

Likewise, IRBs and institutions need to make certain researchers and faculty are aware of the difference between research that needs to be reviewed by the IRB and classroom exercises that do not.

"On the other side of the pendulum, there are some principal investigators who are professors who assign research to students that becomes real research and is designed to contribute to generalizable knowledge throughout the world and is designed to be published," Pospisil says. "And sometimes those people don't feel the IRB has jurisdiction over their work since they're making it part of their curriculum in their classroom."

Deception and debriefing

Another risk area to consider when reviewing social-behavioral research involves the use of human subjects in a study that employs deception, he says.

"Deception is a thoroughly legitimate area of study, and it involves using human subjects who either, a) may not know that they are subjects or, b) know that they are subjects, but are misled about the purpose of their participation," Pospisil explains.

This type of research needs very careful review, and precautions need to be built into the study so that if people begin to experience emotional discomfort or severe reactions, there are interventions planned to assist them, he says.

Also, IRBs should consider whether and how investigators would debrief the subjects. In some cases an IRB may decide that it would be better to not let subjects know the true nature of the research in which they were involved, while in other cases subjects would be told the truth in a very careful and sensitive manner, Pospisil says.

"A scientific study might create situations in which people would do things they wouldn't normally do or approve of doing," he adds.

To minimize risk in social-behavioral studies, Pospisil makes these recommendations:

- **Advise investigators to use procedures and alternatives that may be less risky.** "For example, in some cases someone conducting research may wish to interview people in a group situation, and the group situation may cause undue embarrassment, so an alternative is to interview people separately," he says.
- **Use precautions and procedures to decrease the likelihood that harms will occur.** IRBs should look at questionnaires as part of the review process and assess whether they might trigger serious emotional reactions, Pospisil says.
- **Have safeguards and procedures in place to**

deal with harms when they do occur. "If you think people may have a reaction to the study, then you should have a psychologist or counselors available," he says. ■

IRB educates community on research, builds trust

IRB member volunteers time to teach

Thanks to the volunteer work and sponsorship of community advocate and IRB member **Isaac Hopkins** of Plainfield, NJ, there is an inner-city Little League team where the 7- and 8-year-old players wear T-shirts that say, "Do No Harm."

"Kids ask me what it means, and I say, 'Do no harm' will take you all through life," he says.

This is just one example of the community outreach, education, and teaching-through-example that has been a hallmark of Hopkins' 15 years serving as a member of IRB at the University of Medicine and Dentistry of New Jersey (UMDNJ) in Newark.

"Isaac Hopkins is the star of the show," says **Barbara LoDico**, CIP, BS, executive director of Human Subjects Protection at UMDNJ.

"He's been in barber shops, schools, churches — pretty much anywhere anyone has asked him to speak," she says.

Inspired by Hopkins' dedication to inform the public about research and building good will through his volunteer outreach efforts, the IRB has developed a formal community outreach program.

The program's funding comes from a National Institutes of Health grant that is intended to support human subjects protection programs, LoDico reports.

The program's goal is to increase public knowledge about research and IRBs and build community trust. Anecdotal evidence suggests its impact has been positive, she says.

"Our calls to the IRB have gone up with people asking more questions," LoDico says.

This suggests that some local citizens who have been recruited for research studies possibly learned about research and IRBs from the community outreach and therefore were comfortable calling the IRB for additional information, she explains.

Hopkins, who has been a community volunteer and member of public boards for more than five decades, has a personal interest in human subjects research and education.

An asthmatic child, he was restricted in his activities and spent many hours in emergency departments, he recalls. "One wish I had was that I could go three days in a row without getting sick, and then it happened."

When Hopkins was nearly 18 years old, medical research led to treatments for asthma that made a major difference in his life, so he has positive feelings about research despite some of the abuses with which he also is familiar.

In 1949, Hopkins served as a chairman of the parole board for the New Jersey State Training Schools for Girls and Boys. He also has worked as a certified crime prevention officer and a parole and hearing officer and drug educator. As a result of his exposure to prisons and prisoners, he learned firsthand about some of the research abuses that occurred in the 1950s, Hopkins recalls.

"I came across a lot of people who were transient and in prisons at one time or another," he says. "I found out some of them were grotesquely disfigured by some of the experiments that occurred before the Belmont Report."

This balanced view of research's public good and, at times, individual evil have helped Hopkins relate to the fears and concerns many people, including some in Newark's minority communities, have about participating in human subjects research.

"I usually just present information and I make sure people know that I'm not a research recruiter," Hopkins says. "I explain what the IRB is all about, and I tell people how the IRB board has scientists, ethicists, clergy, and community members."

Calming fears

Hopkins also explains that the IRB has members who are sensitive about cultural issues and who are very concerned about how research participants are treated during the informed consent process.

Usually when he is speaking before the African-American community, people know about the abuses in the Tuskegee (AL) Syphilis Experiment (conducted by the U.S. Public Health Service between 1932 and 1972), so Hopkins will explain how there have been a number of laws passed to better protect people participating in research.

"I talk about the risk-benefit ratio, and I say that the key thing is to make sure that if they participate in any research that they ask all of these questions," Hopkins says. "I tell them that they can wait two or three days until they get the right information and that it's not necessary for them to participate before they know what's going on."

The goal for him and the IRB is to build trust in the Newark community where a great deal of research occurs.

"It's been pretty easy for me to engender trust because I've been working with folks for a long time," Hopkins says. "Trust sometimes is based on the person delivering the message rather than what is actually happening."

Another aspect to building trust involves the reputation of the institution that is conducting research, he adds. "We're the largest and have one of the best trauma centers."

So when Hopkins discusses UMDNJ, he knows people associate it with a competent, technologically advanced institution that they would trust to apply the highest standards to scientific research, Hopkins says.

Hopkins also believes in educating young people about research. Besides his Little League sponsorship, he has helped to establish a faith-based health and disability initiative in which 15-20 students are assigned research projects that will teach them about disabilities and health and give them exposure to research.

"Each one has an assignment to go to a web site and find out about a particular disease, such as tuberculosis, AIDS, hepatitis C, etc.," Hopkins says. "Then at the next meeting, they report back to us."

Although having an IRB member who has decades of community volunteer experience and is considered a community leader is an ideal way to connect with and educate the public, there are several other ways that IRBs and institutions can educate and build public trust.

Outreach efforts

LoDico lists these programs that the institution has started to promote community outreach:

• IRB members participate in a medical lecture series. Research education is included in the UMDNJ's annual medical lecture series for the public.

Attendees may listen to medical school professors discuss issues similar to what they might teach their students. Some of the lectures during this eight-session course may include innovative research techniques, human subjects rights, and ethics, LoDico says.

"One year, we turned the community [attendees] into mini-IRBs and gave them case histories to review," she says. "Another year, we turned them into mini bioethics boards with research questions, and they had to decide how to handle them."

Through this lecture series, people who have volunteered to be community members of the IRB, LoDico adds, have approached the IRB.

"The lecture series exposes the community to the types of discussions that happen when they're evaluating a research study," she says. "Many people think the medical community acts in a vacuum, but this demonstrates that the community has a voice and the regulations require it."

• The IRB's research brochure has been translated into various languages. The Newark community includes Portuguese, Spanish, and other ethnic groups, so when the IRB's research brochure has been translated into these languages, as well as Braille, LoDico says.

The brochure often is given out when Hopkins or other IRB members speak before community groups, such as religious organizations. And it's left in public areas of medical units and is handed out at health fairs.

The brochure discusses human subjects research protection, defining what research is and what the rights are for research participants, LoDico says.

• The institution held a workshop on human subjects protection. One of the most successful community educational ventures was a workshop held in May 2001 in which 200 people attended a two-day workshop about IRBs and human subjects protection, LoDico says.

One of the IRB's goals is to start a lecture series that will cover a variety of IRB and research topics, including adequate consent process, community interest in research with the elderly, and people with the inability to give consent, she says.

"This could be a mentoring program for the community to introduce them to how it is to be an IRB member," LoDico says.

While the series could result in more volunteers for the community member positions on IRBs, its main goal is to educate the public and to give them the information they need to make informed decisions about participating in human subjects research, she says.

"It really bothers me to hear that people are afraid to participate in research," LoDico says. "I think they should say 'No' because they want to and not because they're afraid." ■

Have you reviewed your IRB policies lately?

OHRP's QI program could help

IRBs may think their policies and procedures have covered all federal and state regulations, but in the experience of federal officials, there commonly are some lapses.

For that reason, IRB regulatory experts recommend that IRBs update and revamp their policies, sticking close to the intent and language of regulatory rules.

"In the regulations there are seven required policies and procedures, and usually [research institutions] are missing a couple," says **Judith Brooks**, MS, public health analyst in the Division of Education and Development of the Office for Human Research Protections (OHRP) of Rockville, MD.

OHRP has a quality improvement (QI) program in which research institutions and IRBs voluntarily may be visited and checked for compliance with federal rules and regulations. The program, which provides consultation but not actual compliance auditing, has resulted in more than 60 QI visits so far.

Based on those visits, there often are policy gaps in at least two regulatory areas, Brooks explains: the policy for determining which projects require review more often than annually and the policy for determining which projects need verification from sources other than the investigator to show that no material changes have occurred since the previous review.

One way to avoid these mistakes is to rewrite policies in a language that stays close to the wording of the federal regulations, suggests **Robert Bienkowski**, PhD, executive director of research at Iowa Health-Des Moines.

"At this institution, we thoroughly revamped our policy," he says.

Beginning in 2002, Bienkowski organized a working group that looked at the institution's current policies and procedures and compared them with federal regulations, as well as with policies at other research institutions.

"The working group rewrote and revised the policies," he reports. "We literally incorporated the federal regulations into the policies and procedures and then took all the relevant steps to indicate how the federal regulations would be implemented."

Also, the working group incorporated state regulations into the policies when these imposed additional requirements. "In addition, the IRB was empowered to become much more proactive in its responsibilities," Bienkowski says.

"If you look at the policies and procedures of other institutions you do have the federal regulations included, but people take bits and pieces of it and rewrite parts of it, and it gets mixed up," he says. "It doesn't flow in a straightforward way as the regulations do, so my operational approach is that the regulations are what the government wants, and so these are written [directly] into our policies and procedures."

Ongoing endeavor

The working group met separately from the IRB on a monthly basis, beginning in May 2002 and completing the revision in January 2003, Bienkowski says.

"It took about eight months for the policy to be rewritten. [We went] through multiple drafts, and then it was presented at the IRB meeting for their consideration," he says.

IRB members who had not participated on the working group had some insightful comments that also were incorporated into the policies and procedures, Bienkowski adds.

Once the revised policies and procedures were complete, the working group was made a permanent entity so that it could update the policies when needed and to handle some aspects of the IRB's work that could not be handled at the regular IRB meetings, he says.

Also, there often are new interpretations of rules and new guidance for regulations, and these may require the institution to review its policies from time to time.

For example, although the institution does not engage in prisoner research, the IRB soon found that it was necessary to have a policy that addresses prisoner research. In one study, there was a subject who became incarcerated after beginning participation in the study, Bienkowski says.

"We didn't know what to do," he recalls. "The investigator took it to the IRB, and the IRB said there are regulations about prisoner research and there has to be a prisoner advocate, so let's disenroll the subject from the study."

This raised a question among IRB members about what would happen the next time this unusual circumstance occurs.

"So now we're developing contacts with the sheriff's office so that we have in place some

procedures to be activated when we need them in order to offer appropriate treatment to a subject who has become incarcerated," Bienkowski explains. "Even if it's necessary for the person to be disenrolled from the study, the person may need treatment."

This scenario was something IRB members never imagined when they wrote the policies and procedures, he says.

"We probably won't go so far as to have a prisoner advocate, but we'll have policies and procedures in place to show what will happen if a subject becomes a prisoner," Bienkowski says. "And in the case of an exceptionally urgent situation, the IRB chair or I will have the authority to tell the investigator that the person should be disenrolled."

QI incentive

While IRBs could benefit from revising policies and procedures to avoid these types of uncommon scenarios, another good reason for dusting off the policy books is to avoid compliance problems in the case of an OHRP not-for-cause visit.

OHRP compliance officials will randomly choose institutions to audit, and they look at the exact same material that the OHRP consultants in the QI division reviews in the voluntary program, Brooks says.

"We have had some serious problems that have closed down institutions," she says.

One way to avoid a not-for-cause visit is to voluntarily participate in the QI program of OHRP, Brooks says.

QI consultants do not share any of their findings with the OHRP compliance officials, nor do they even keep documentation of any of their findings, but they do share the names of the institutions that they visited, she says.

"If you had a recent QI visit then you would not be identified as a not-for-cause visit," Brooks explains. "We make sure [OHRP compliance] knows who we are going out to visit so they won't go back to the same place in three months and do the same thing."

This also gives institutions time to make changes according to the QI consultants' recommendations.

"The reason we're encouraging participation in the QI program is because the push for accreditation is rising, and this is a nice place to start with the IRB component of it," Brooks says.

"Accreditation involves the whole human subjects protection program, and this way they know their policies and procedures are in good shape before they become enrolled." ■

Grasp of genetics basics makes IRB review easier

Expert offers genetics primer

More institutional review boards are seeing proposals for studies involving some type of genetic research, but many IRB members feel unprepared to appropriately review the study design and assess the potential risks involved.

Because experiments that involve analyzing or manipulating genetic information can pose novel risks to human subjects and because members have often not had sufficient education about genetic principles and terms, they tend to be very cautious when reviewing these protocols, says **Barbara Handelin**, PhD, the CEO of Kenna Technologies Inc., a drug discovery company in West Chester, PA.

In 2000, Handelin, a trained geneticist, helped conduct a research study funded by the U.S. Department of Energy that evaluated the challenges IRBs faced when reviewing genetic studies.

"What you very quickly hear, if you sit down in room with a dozen or so IRB folks and ask them about their concerns involving a genetic protocol, they will very quickly list for you 25 issues or questions that are somehow related to genes, but only about 10% of them would be relevant for any given protocol," she says.

For example, concerns about gene transfer and heritability of altered DNA are not relevant to family studies designed to discover genetic traits that might indicate an increased risk of developing disease because gene therapy will not be administered and no changes in anyone's genetic makeup will take place.

Likewise, concerns about the revelation of genetic information about family members are not usually relevant to gene modification studies, Handelin adds.

And while it's true that some genetic protocols can present unusual risks for study participants, in many cases the risks presented are the same or very similar to concerns that other biological studies raise, she adds.

Privacy issues

A concern frequently cited in conjunction with gene studies is that genetic information obtained about one person also reveals information about

that person's family members.

However, that also is true to some extent, in infectious diseases research studies, she notes. Therefore, procedures that would be used to address privacy in those studies might also be helpful in studies involving genetic information, she says.

"The other common comparison that we make is with tumor registries," Handelin adds. "They've been doing those for decades. You have these huge databases of people with cancer, and you know, for many years it was never disclosed to people who: a) they were in a tumor registry; and b) what was going to be done with that information, and that, in fact, the information was not anonymized."

The key issue that distinguishes studies that involve analyzing genes vs. other types of research, Handelin says, is the potential for genetic information to be predictive of future disease.

"The two biggest impacts that we expected from our ability to understand the genome better were: a different way to define disease because we would recognize more specific causes of disease, there would be a new way to do differential diagnosis; and we would more specifically define diseases that we had mischaracterized or lumped together because we had only been able to see the effects or the pathology of the condition and not its molecular bases," she says. "The second concern, is that it is really different when you begin talking about future disease. Medicine, traditionally, is a totally reactive discipline, people have illness and you try to respond. Preventive medicine is sort of the Holy Grail for genetics, but there are complications associated with finding out about something before it happens."

Different types of genetic research

To more accurately evaluate the potential risks and benefits to human subjects of a particular research trial involving genetics, it might be helpful for IRBs to have a system for triaging the proposals, or categorizing them according to the type of genetic information that will be analyzed or manipulated, Handelin says.

In doing so, the IRB can then be sure to evaluate the risks that are posed by that type of research and discard concerns that are not relevant.

Genetics research can be categorized into three basic types of studies, she says. These are:

• **Family studies** — Studies in which specific families are recruited based on the high prevalence of a genetic trait in the family. Twin studies are one type of family study, and familiar examples of family studies include the searches for genes causing Huntington's disease, the breast cancer gene BRCA1, cystic fibrosis, manic depressive disorder, or the high-iron disorder, hemochromatosis.

• **Population association studies** — Investigators seek an association between a particular genetic marker (a polymorphism) with a trait by analyzing the coordinate presence and absence of a genetic marker and the trait of interest in a broad population of unrelated individuals. The structure of the study is the same as any statistical correlation study; the only thing setting these studies apart from the traditional ones is that the subjects' genome is being analyzed as one of the correlates.

Add-on genotyping studies in a drug trial are a typical type of population study seen today. Large studies of archival tissues in which a wide variety of genes or random genetic polymorphisms are going to be analyzed are another common type of population association study.

Familiar examples of population studies include: Alzheimer's disease association with the ApoE4 polymorphism; association of violent behavior with gene markers; association of another ApoE4 variant with heart disease.

• **Gene modification studies** — These studies include any study that involves the transfer of an external gene into a human subject regardless of whether there is going to be modification of the subject's genome, which is rare.

Genes are modified by installation into a delivery vehicle (vector) that serves to transfer the gene into cells and upon delivery are intended to modify the activity of the cell in some way. These studies are often called gene therapy, which is misleading in that it implies that the genes are the target of the therapeutic effort rather than being the therapeutic product themselves.

Familiar examples of genetic modification studies include: treating cystic fibrosis with the CFTR gene; treating ornithine transcarbamylase deficiency (OTC) patients with the OT enzyme gene.

Evaluating the risks

Once the studies are categorized, IRB reviewers can proceed to considering the list of risks relevant to that type of genetic research.

IRBs should share their lists of the relevant

risks with investigators at their institutions in advance of receiving protocols, Handelin adds.

The potential risks involved in the different categories of genetic research[1] are listed below:

Family Studies — aspects of family studies that determine specific potential risks:

- Subjects are members of the same family, sharing genetic traits frequently.
- Investigators may intimately know some family members and be strangers to others.
- Recruitment may be convenient at family reunions or other family gatherings.
- Individual subjects may have the trait under investigations or may not; their membership in a family may be the only connection to study the study.
- The trait under study may be a significant part of the family's identity and dynamics, including familial and parental guilt, anxiety, honor, etc.

Reproductive decisions may be profoundly influenced by the subject of the study especially in the case of major life-limiting illnesses in children.

Potential risks peculiar to genetic studies conducted on related subjects:

- ***Coercion in recruitment:*** Since the family is identified as a desirable set of subjects through perhaps a single affected member, recruiting other family members must be conducted carefully to avoid coercion by family members.
- ***Risk to reveal nonfamilial relationships*:** Since multiple family members will be studied using genetic markers that are purposefully chosen to reveal both relatedness and differences between family members, there is a high likelihood that false familial relationships will be uncovered (nonpaternity, nonmaternity, nonsibling, etc). Subjects must be informed and a policy set forth on whether this type of information will be shared with any participants.
- ***Family dynamics*:** Recruitment and the study itself will be conducted in the context of family emotional and psychological dynamics. Since genetic traits are transmitted from parents to offspring, a range of emotions from guilt to pride in such sharing of traits between generations can be a powerful component of family dynamics. How does the protocol recognize and manage this aspect of recruitment and ongoing relations between the principal investigator and subjects?
- ***Reproduction*:** In studies, especially involving highly morbid diseases in children, subjects or relatives of subjects may be undergoing reproductive decision making that may be seriously impacted by either new information created through the study or by the increased focus within the family on the disorder. How does the protocol address this sensitive issue?
- ***Familial privacy:*** Since genes are shared between relatives (50% of genetic variants between first-degree relatives, 25% between second-degree relatives, and so on), if one subject obtains information about their genetic status, relatives may believe that they too have received information on their own genetic status by inference. How does the protocol deal with the risk of inadvertently conveying gene status information beyond the direct subject?
- ***Publishing pedigrees*:** Since publishing results is a desirable outcome of all research, the investigator needs to proactively address how familial information will be presented in the public press so as to protect the anonymity of the family subjects. For example, publishing pedigrees is necessary when reporting on a family study, but even if names are omitted, family members will easily recognize themselves and others along with deriving genotype information from a published pedigree. This breach of privacy must be avoided.

The American Society of Human Genetics has published guidelines on modifications to pedigrees that do not compromise the reporting but which mitigate the likelihood of Uncle Steven discovering the genotype of his estranged daughter without her consent.

- ***Right not to know*:** Persons may volunteer to participate in a family study as a subject but may have a deep commitment to not learning any genetic information about themselves (or others) that results from the study. (Indeed, this can be a strong reason for not participating at all.) This degree of privacy and one-way communication of information (only from participant to investigators) must be made available and a special side protocol may even be necessary to adequately provide assurances to such subjects.

Population Association Studies — aspects of population studies that present specific risks:

- Fishing expedition nature of many correlation genetic studies.
- Identifiable populations may have undesirable genetic correlations reported as results of the study.
- Use of stored tissues as sources of DNA is common in these protocols.
- Traditional drug trials are increasingly

including genetic studies as add-ons.

• Having access to longitudinal clinical information enables many (if not most) correlation studies.

• Evergreen characteristic of DNA as the lingering remains of subjects creates future opportunities for research beyond the duration of the current protocol.

Potential risks to subjects:

• ***Access to personal genetic information:*** Many population based genetic studies have an open-ended protocol that includes the possibility that genotype information could be discovered about an individual's health sometime in the future. Because DNA can be stored virtually forever, the samples are everlasting. Subjects need to be informed as to whether they will be contacted about such information at any time and why or why not.

• ***Unknown future studies:*** Because DNA is a very stable sample and because technology continues to improve for both sparing and creating a renewable DNA sample, this material from subjects can become an everlasting resource for research. Many population-based studies will therefore include a proposal to maintain this rich experimental resource for future — as yet to be determined — research. Subjects should be informed about such future use when donating a new sample, in the context of the degree of anonymity afforded by the protocol.

• ***Group stigma:*** Population based studies may be designed around the prevalence of a genetic trait in certain defined populations: ethnic groups, gender or behavior-driven groups, etc.

If results about the population become publicly available and the results reflect a defective or undesirable attribute associated with the group, then the entire group, as well as individual members, is at risk for stigmatization and potential discrimination. Investigators need to provide a plan for how such group stigmatization will be avoided in handling both publishing and presenting all data.

Genetic Modification Studies — aspects of genetic modification studies that create specific risks:

• These are therapeutic experiments, or trials; they are thus in a different category from family studies or correlation studies in that subjects are being treated with unknown compounds as opposed to having their genome analyzed.

• DNA (gene) is a "living drug" in that it is a natural, integral part of all cells in all living beings.

• Genes are completely novel compounds compared to all other drug trials.

• Genes, if they integrate into the genome of the recipient, can be permanent residents of cells.

• There is a small but measurable possibility that the genome of a recipient's germ cells (eggs or sperm) accepts a permanent new gene and then the therapy has the potential to be transmitted to offspring of the subject.

• The delivery vehicles (vectors) are poorly understood and are also biological materials (viruses in some cases, lipids and other materials in other cases) with as yet unproven and potentially dangerous effects on the recipient.

• Some target diseases for early gene therapy experiments are disease of childhood and are inherited; e.g., cystic fibrosis, familial hypercholesterolemia.

Potential risks to subjects in gene modification studies:

• ***Clinical management of subjects*:** Gene therapy experiments typically bring a basic researcher with expertise in genetic manipulation and gene transfer to developing an interest in treating a clinical disorder. As such, the investigator is making a significant move into clinical research and clinical treatment with often very little training in either domain.

Moreover, gene therapy experiments are often to be conducted in subjects with a rare disorder (e.g., cystic fibrosis, ornithine transcarbamylase deficiency, familial hypercholesterolemia, etc.) where clinical expertise in caring for such patient subjects can be equally rare.

Risk to subjects is created when such subjects with peculiar clinical issues are being treated,

COMING IN FUTURE MONTHS

- Develop plan to better manage IRB workload
- Distinguish between quality improvement and research
- Analyzing the IRB's role in data and safety monitoring plans
- Asking the right questions when it comes to secondary subjects

followed and managed by clinically naive investigators. IRBs should be thorough in evaluating and requiring the clinical appropriateness of investigators in any gene therapy trial, especially in trials involving rare disorders.

• ***Children as subjects*:** Some diseases that have been the focus of early gene therapy diseases occur in children and thus have the usual special risk issues of having children as subjects.

• ***Family dynamics*:** Many early gene therapy experiments have been conducted in disorders caused by faulty single inherited genes.

• ***Changing the blueprint of life?*** IRBs need to be clear about which types of cells is the target of the gene transfer; germ cells (eggs or sperm) or nongerm cells (all other cells, called somatic cells).

Nongerm cells do not have the potential to be passed on to offspring of subjects who receive a new gene; thus this is not a relevant risk for most protocols. However, IRBs are advised to query investigators about their evidence that germ cells not inadvertently be subject to gene transfer in the proposed experiments.

• ***Pre-clinical studies*:** Because gene transfer is a relatively new therapeutic method, pre-clinical studies in tissue culture and animals may be difficult to gather with the same depth or rigor that is seen in typical drug trials. Yet there are large potential risks to subjects from the unknown effects of the gene delivery vehicle and the gene drug. Thus, IRBs should obtain consultation on the relevancy and rigor of the pre-clinical studies that support each protocol.

• ***Unavailability of proven therapy*:** The unavailability of alternative treatments for rare disorders may make potential subjects and their families desperate to volunteer for any experimental trial however novel and unproven.

Special care should be taken to explain to subjects the preliminary nature of such research, the uncertainty of risks and remote possibility of benefit especially to those involved in early trials. Investigators may have to involve third parties in the consent process to guard against the potential for unintended coercion.

Reference

1. Excerpted from: *The Responsibility of Oversight in Genetics Research: Issues for Institutional Review Boards in Reviewing Genetics Protocols, Part II: Triage for IRB Review of Genetics Protocols.* Developed by Barbara L. Handelin, PhD, and Susan Katz, JD. Supported by a grant from the U.S. Department of Energy Human Genome Project Grant #DE-FG02-98ER6245. ■

Reader Question

IRB mergers can be smooth with planning

By **Paul W. Goebel Jr.**
Vice President
Chesapeake Research Review
Columbia, MD

Question: Our institution's IRB is merging with another IRB. What can we do to make the transition efficient? (In other words, what can go wrong and how can we minimize the possibility?)

Answer: The question presents a situation where two hospitals or medical centers wish to merge the two IRBs into one.

Mergers of this type can be done relatively smoothly if you keep in mind the following:

• The terms of the merger must be outlined in writing and agreed to by the decision makers for each institution.

• If either of the institutions conducts federally funded research, the assurance that it has filed with the Office for Human Research Protections must be amended.

• The populations from which each institution draws study subjects should be examined for dissimilar cultures. The IRB membership and the IRB staff should be sensitive to minority populations that are likely to participate in studies reviewed by the new IRB.

• If the institutions are in different states, the merged IRB must be aware of each state's requirements for IRB review and informed consent and assure the new/transitioning IRB procedures are in compliance.

• Each institution is likely to have different operational policies, constraints, and commitments. The IRB administrator, in concert with the administration of each institution, must develop a policy and procedure manual that represents the expectations of the new entity.

• The examination of processes should extend to such areas as control and accountability for the investigational test articles including receipt at the institution, secure storage and records of distribution or disposition. ■

CE/CME objectives

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

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **describe** the regulatory qualifications regarding human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research;
- **apply** the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- **explain** the potential for conflict of financial interests involving human subject research;
- **discuss** reporting adverse events during research.

CE/CME *questions*

Physicians, nurses, and others participate in this continuing education program by reading the article, 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 in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

17. When a biomedical IRB reviews a social-behavioral research protocol, which of the following types of risks often is overlooked?
A. Cultural and privacy
B. Social, economical, financial, and psychological
C. Physiological and genetic
D. All of the above

18. The Office of Human Research Protections has found that IRBs often have gaps in their policies and procedures, particularly in which of the following areas?
A. The policy for determining which projects require review more often than annually
B. The policy for determining which projects need verification from sources other than the investigator to show that no material changes have occurred since the previous review
C. Both A and B
D. None of the above

19. Three basic types of genetic studies include which of the following:
A. Family
B. Population association
C. Gene modification
D. All of the above

20. Concerns about gene transfer and heritability of altered DNA are relevant to family studies designed to discover genetic traits that might indicate an increased risk of developing disease.
A. True
B. False

Answers: 17-B; 18-C; 19-D; 20-B.

IRB ADVISOR
Your Practical Guide To Institutional Review Board Management

Salary increases are flat, but growth outlook is good

Research compliance is serious business, particularly when your studies involve humans. So serious, in fact that federal regulations exist, review boards have been developed to oversee the process, and organizations have sprung up to offer education and support to research professionals.

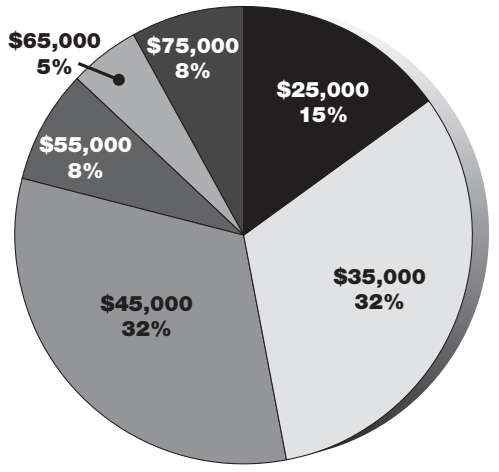
This summer, *IRB Advisor* took a focused look at the professionals who on a daily basis oversee compliance efforts. We are pleased to present the results of the 2003 Salary Survey for IRB Professionals.

Respondents were diverse — titles ran the gamut from IRB Coordinator to Regulatory/Compliance Officer to Vice President of Research Development. There were Chaplains among respondents — median annual income $70,000; Research and Clinical Trial directors — median income $53,000, though the salaries ranged from $40,000 to $130,000+; Senior Investigators — median income $95,000; and Medical Ethics Directors — median income $75,000.

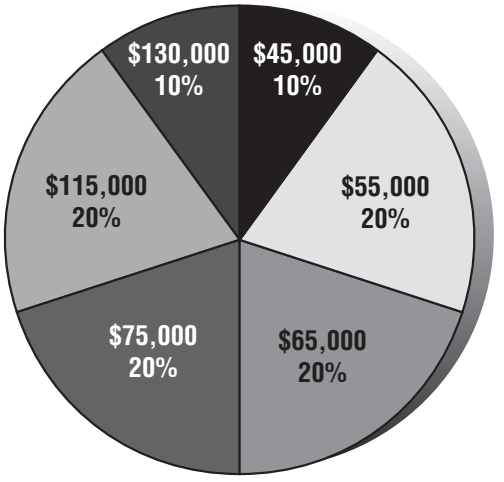
One factor was common, however, across title categories: The average wage increase percentage was 1% to 3%. One respondent in the Research Development area received a 21% increase; and a handful of Compliance Officers received increases in the 11% to 15% range. But 53% of respondents received 1% to 3% wage increases, and 14% reported no annual increase.

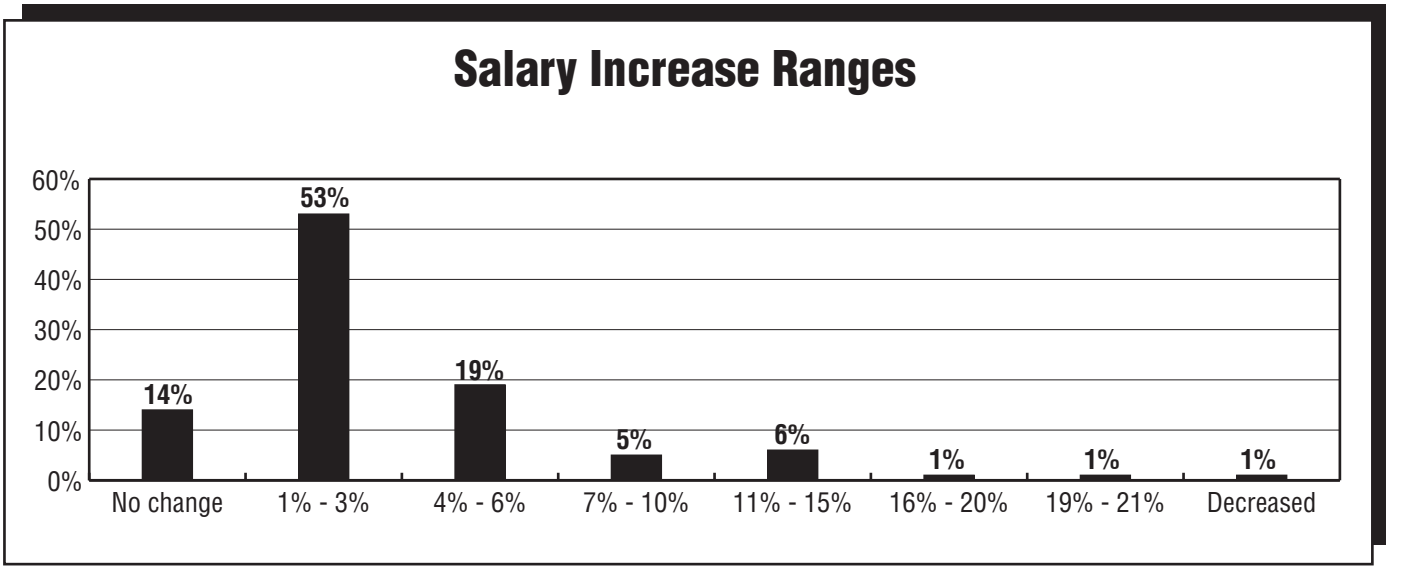
Data also revealed what many of you already know: IRB-related work is not a 9-to-5 effort. The majority of respondents are working long hours. Though 10% of respondents reported

IRB Coordinator/Administrator/Manager Median Salary Ranges



IRB Director/Chair Median Salary Ranges





working 20-30 hours per week, four out of five professionals — 80% — worked 46 or more hours per week.

"I work 50 to 60 hours per week," says **Lynn Bevan**, administrative director for research regulatory affairs at The Children's Hospital of Philadelphia. She's not alone. In fact, 20% reported working 65 or more hours.

Growth looks promising

If the number of clinical trials being conducted is any indication, the job outlook for IRB professionals is good. The National Institutes of Health (NIH) alone currently has more than 7,000 clinical trials listed on its ClinicalTrials.gov web site, and its 2004 proposed research budget is an estimated $67 billion, up $3 billion over the 2003 budget.

The Pharmaceutical Research and Manufacturers of America reported in its 2002 Annual Survey that pharmaceutical companies spent $30 billion on research and development in 2001, and had more than 1,000 medicines in development going into 2002.

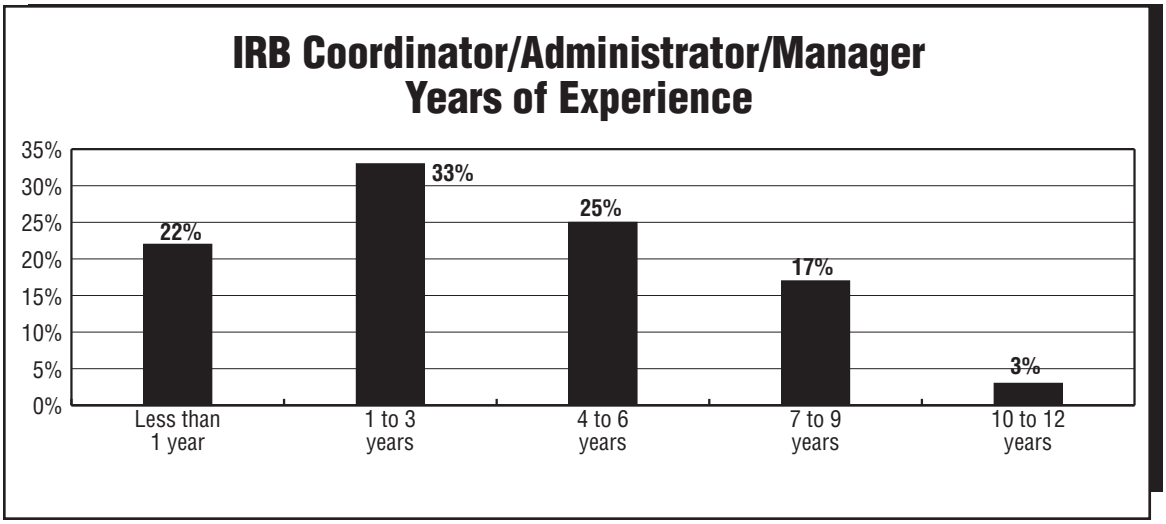
Additionally, genomic discoveries and resulting products being developed surely will increase the need for qualified professionals who can oversee human subjects protections programs.

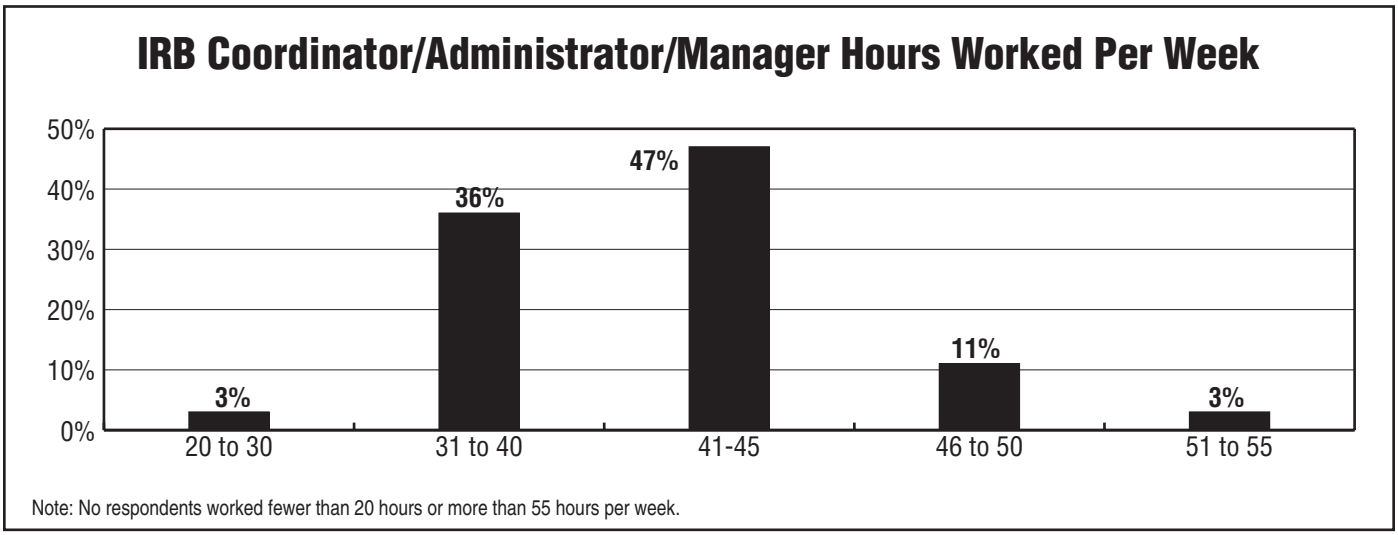
"Go to IRB web discussion groups, and you can see there is a large need and market for IRB professionals," says **Susan Kornetsky**, MPH, CIP, director of Clinical Research Compliance at Children's Hospital in Boston. "IRBs have been around more than 20 years; but as recently as five to seven years ago, organizations and institutions didn't realize that IRBs needed to be supported. In the past, maybe one or two people supported the IRB. Now, at larger institutions, 15-20 people are on the IRB staff."

Many still are trying to fill slots, Kornetsky says. A quick Internet search supports her assertion. The IRB Forum (www.irbforum.com) job board has posted 86 research-associated ads since January. Of those, 31 were IRB-related positions, including listings for administrators, assistants, coordinators, managers, specialists, and a regulatory auditor. A recent search on the employment web site Monster.com yielded more than 1,000 responses to a "medical research compliance" job query.

Median Salary by Title

Clinical Research Coordinator	$50,000
Human Subjects/Protections Administrator	$57,500
Compliance/Regulatory Administrator	$57,000
Director, Clinical Trials Research	$68,000
Research Manager	$75,000
Regional Director, Compliance	$115,000
Vice President for Research	$130,000





"In the past, no one know what an IRB administrator did," says Kornetsky, who says she is beginning to see more qualified applicants.

"The IRB administrator is a liaison between the IRB and the research faculty," Kornetsky points out.

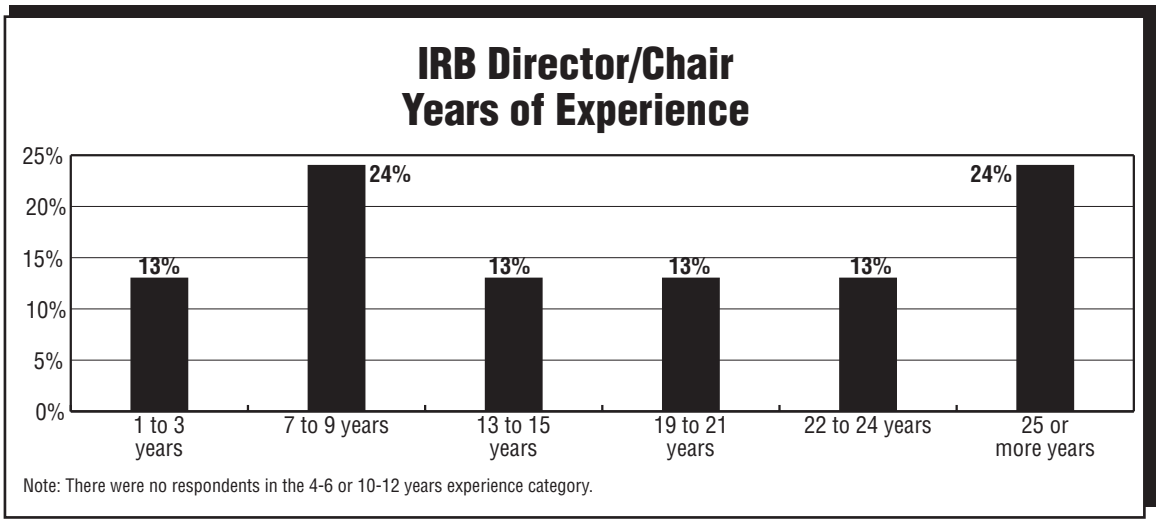
"Of course they have to understand the regulations, but they must also have good communications skills. They must understand what it means to be an investigator trying to do research," she adds.

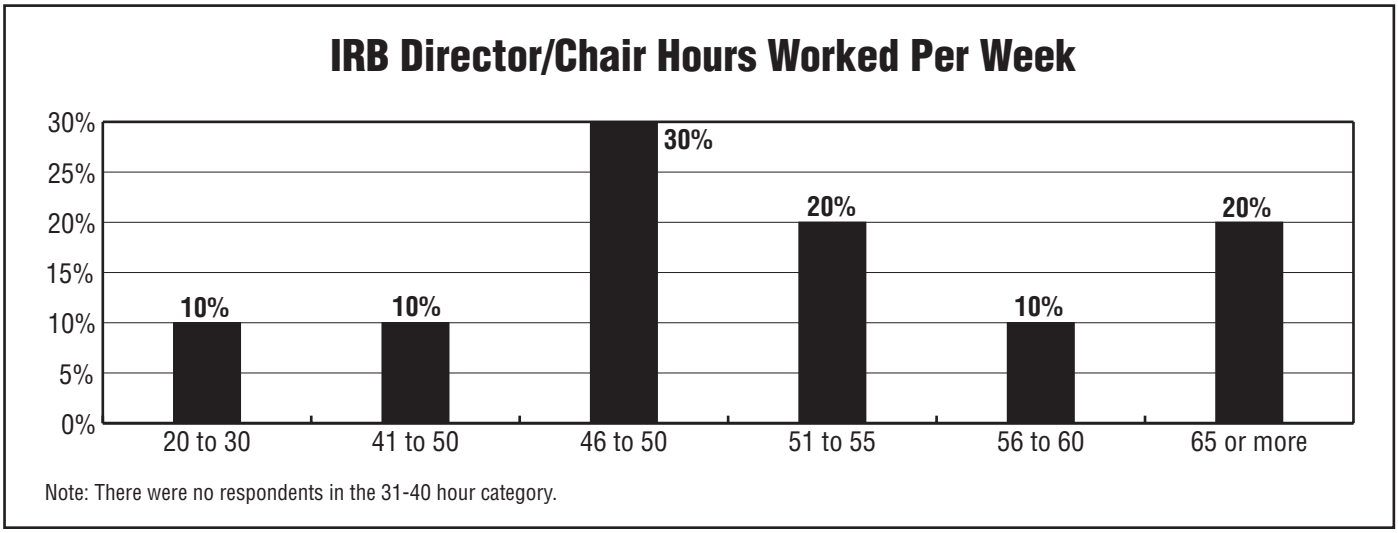
Kornetsky looks for people who have good people skills, as well as some experience with research or human subject protections. She says she received 10-15 resumes the last time she had an IRB administrator position open, and at least seven were qualified applicants.

Helen McGough, MA, CIP, director of the Human Subjects Division at the University of Washington in Seattle, lists the following as required skills:

- a thorough understanding of the regulations and policies (international, national, state, and local) protecting human subjects in both biomedical and social science and behavioral research;
- the ability to manage staff in an environment of limited resources;
- the ability to communicate complex regulatory issues to a variety of audiences including research subjects, researchers, research staff, institutional administrators, and sponsors;
- a good understanding of ethics and a willingness to stand firm in their defense.

"The pool of skilled IRB professionals is small, but growing," McGough says. "Five years ago, it was very difficult to recruit anyone with direct IRB experience. As institutions have expanded their staffing for this function, it has become easier to find people with some IRB experience. In another five years, I expect that we will have a wider and more experienced pool of professionals."





Certification may up increases

In October of 2000, the first certification test for IRB professionals was administered but it's not clear yet whether CIP (certified IRB professional) designation will result in higher wage increases going forward. "I think if someone is certified, it may hold more water when requesting a salary increase," says Bevan, "but years on the job play more of a role in my mind."

Janine Beal, IRB coordinator, HIPAA, Children's Hospital of Philadelphia, agrees. "Certification may play a small role, however, I believe job performance plays a bigger role," she says.

Kornetsky notes, however, that some of the job descriptions she's seen posted are requiring CIP certification, and she thinks that's a good thing. "CIP certification ensures that IRB professionals share a common body of knowledge," she says. Kornetsky serves on the Council for Certification of IRB Professionals, which is a part of ARENA/PRIM&R (Applied Research Ethics National Association and Public Responsibility in Medicine and Research), and helped develop the certification test. "It's our hope that certification will bring value to the individual and institution," she says. "It's new, so only time will tell."

Kornetsky says she knows of at least two institutions that offer a salary increase to those passing the CIP certification exam.

Regardless of the CIP status, there seem to be more IRB-related jobs than people to fill them, Kornetsky points out.

"Employers are looking for IRB professionals who will assure that research conducted within the institution is ethical and regulatorily unassailable," says McGough. "I expect that there will continue to be growth in the field over the next five years as institutions become accredited and as research dollars continue to expand. I think institutions, both academic and nonacademic, have come to realize that although compliance is expensive, noncompliance is even more expensive." ■