IRB ADVISOR

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INSIDE

Maryland reviews research policies after paid PI reports no COI

Nearly $230,000 refunded; COI training mandated

By Gary Evans, Senior Staff Writer

An investigative committee at the University of Maryland (UMD) in College Park has recommended mandatory education on conflicts of interest for research faculty and advised an IRB to revisit its expedited review and informed consent waiver policies.

The action comes after a principal investigator (PI) failed to disclose any conflict of interest (COI) despite receiving funding from the makers of an enhanced high-protein chocolate milk product that was the subject of his research on exercise and cognitive function. The PI declared no conflict of interest and the IRB approved both phases of the trial on expedited review, waiving informed consent in the second phase of the study.

"Mandatory, in-person training on the principles of what constitutes a COI in research and why it must be disclosed should be required for all faculty, staff, and graduate students working on funded research or service projects," the ad hoc committee recommended in a recently released 14-page report.

> "MANDATORY, IN-PERSON TRAINING ON THE PRINCIPLES OF WHAT CONSTITUTES A COI IN RESEARCH AND WHY IT MUST BE DISCLOSED SHOULD BE REQUIRED FOR ALL..."

The IRB at the university was also advised by the committee to "review its current practice of expedited review and/or approval of a waiver of informed consent in cases in which the protocol involve an intervention with human subjects, even though the potential for harm is minimal, another

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entity will be collecting the data, the data are de-identified, and the PI is not directly involved with the subjects."

The first phase of the study was approved under IRB expedited review in part because it was non-invasive and primarily used a questionnaire. The second phase of the study, which involved cognition measures of high school football and women's soccer players, was also granted an expedited IRB review. Moreover, the second phase included a waiver of informed consent to high school football players because drinking the milk was considered low risk, the students would not be identified, and the PI would have no interaction with them, the committee reported. The panel recommended that the IRB that approved the study under an expedited review revisit the policy.

"Of particular importance is an [IRB] assessment of the scientific merit of the proposal and whether the benefit gained is important enough to justify research on human subjects in general, but especially when the research involves unconsenting subjects and minors," the committee wrote. "This is an important issue both for projects involving service to industry and research designed to contribute to generalizable knowledge through publication in peer-reviewed journals and outlets."

The IRB should review its guidelines for ensuring that participation by student athletes is voluntary, especially where the university Department of Intercollegiate Athletics is actively involved or when all the athletes are members of a single team, the panel recommended. "The committee is concerned that voluntary consent and participation is very difficult to evaluate under these circumstances."

The issue came to light when two press releases reflecting positive but partial results of the study were issued in 2015. Media inquiries revealed the press releases appeared to endorse the product but were not based on peer-reviewed, published research. This raised the concerns of **Patrick O'Shea**, PhD, vice president and chief research officer at UMD, who formed the ad-hoc committee in January of this year.

The charge was to conduct an institutional review of the processes surrounding a study entitled "Muscle Recovery with Fifth Quarter Fresh." The study, arranged through the Maryland Industrial Partnerships (MIPS) program, evaluated the effect of the specialty milk against similar products regarding muscle recovery after vigorous exercise. The second phase was designed to see if the high-protein milk had an effect on cognitive function after mild traumatic brain injury.

The MIPS program promotes the development and commercialization of products and processes through industry/university research partnerships normally initiated by the companies to meet their own research and development goals. Faculty partners may come from any University System of Maryland institution, and funding to support the research comes from both the partner company and the state of Maryland.

The PI for the project is Jae Shim, PhD, associate professor in the department of kinesiology in the UMD School of Public Health and head of the neuromechanics lab. Shim had not responded to *IRB Advisor*'s requests for comment as of press time.

The industrial partner is Fluid Motion LLC, manufacturers of the Fifth Quarter Fresh milk product. Although the committee found

no wrongdoing by Fluid Motion LLC, the university is returning $228,910 provided by the company and Allied Milk Producers "out of an abundance of caution and to remove any perception of conflict of interest," according to an April 1 letter issued by O'Shea after receiving the panel report.

According to the report, Shim saw the funds as gifts for unrestricted support of his lab and disclosed them to his department chair. "However, an email from Fluid Motion to Dr. Shim dated July 18, 2015, makes it clear that their expectation was that the funds were for direct support of research," the committee stated.

The committee reported that "Shim approved press releases in which he directly endorses Fifth Quarter Fresh. In the first press release [July 15, 2015], he stated: 'Our data suggest that athletes may be ready faster and better for the next game or practice if they drink Fifth Quarter Fresh chocolate milk.'"

In a second Dec. 22, 2015, press release, Shim stated, "Athletes who drank the milk [FQF] compared to those who did not, scored higher after the season than before it started, specifically in the areas of verbal and visual memory." The communications offices of MIPS and the University of Maryland relied on Shim's approval for the release, the panel noted.

"Product endorsement attributed to Dr. Shim in two press releases is troubling, but the endorsement does not violate any written university policy," the committee stated. Citing a couple of policies that may apply but were not specific enough, the committee nevertheless made the point that, "it is surprising that a tenured faculty member would think that product endorsement is appropriate."

Press releases should never include study data or conclusions, even preliminary, until they have been subject to peer review and, under most circumstances, accepted for publication in an appropriate peer-reviewed journal or book, the panel recommended.

"The strictest standards for peer review should be applied to research results that are based on human subjects or animals," they stated. "The responsibility for determining that these conditions have been met should rest with the PI, the Department Chair and/or Dean, and MIPS staff. Therefore, the press releases at issue in this matter should be taken down from the university's website immediately."

"WHILE WE HAVE EVERY REASON TO BELIEVE THIS WAS AN ISOLATED INCIDENT, ANY DEVIATIONS FROM ACCEPTED PRACTICES IN THE RESPONSIBLE CONDUCT OF RESEARCH CANNOT BE TOLERATED."

The press releases have been withdrawn and removed from UMD Web postings.

The committee determined that Shim's receipt of funding without reporting a conflict of interest was a violation of university regulations.

"The product endorsement by Dr. Shim and the incorrect statement on the IRB protocol that all tests on the high school athletes would take place whether he was involved or not, and his conversations with the milk company on details of the experiment design appear to us to be significant deviations from accepted practices in the conduct of research," the committee concluded. "In spite of having notified his Chair, Dr. Shim's failure to declare gifts from the Allied Milk Foundation as a conflict of interest violates university regulations. Taken together, these findings raise serious concerns about the PI's understanding of the requirements for human subjects research and suggest the need for appropriate training of Responsible Conduct of Research."

Again, Shim could not be reached for comment during the compiling of this report. Asked about disciplinary action against the PI, a UMD spokeswoman says, "Any potential sanctions against faculty or staff involved in this matter would be considered, by policy, confidential personnel matters."

O'Shea's letter acknowledged the problems identified by the committee and outlined the following actions on some of the recommendations:

•The Division of Research and the Office of the Provost will collaborate to further implement appropriate modifications to university policies, practices, guidelines, and MIPS operating procedures.

• Work has begun with a conflict of interest committee to determine appropriate policies and training programs for all applicable research and administrative personnel.

"While we have every reason to believe this was an isolated incident, any deviations from accepted practices in the responsible conduct of research cannot be tolerated," O'Shea stated.

Editor's note: The UMD committee report is available at: bit.ly/1SNSsuX. O'Shea's letter outlining the UMD response is available at: bit.ly/1RMgS5O. ■

'Optimistic bias' may subvert informed consent in early-phase cancer trials

'Potential harm to patient well-being and autonomy'

There is a gray area where optimism in a research patient in early phase cancer trials crosses over to a misperception of benefit and raises ethical questions about informed consent, says **Lynn A. Jansen**, PhD, associate director of the Center for Ethics in Health Care at Oregon Health & Science University in Portland.

"I have served on IRBs and something we are all concerned with is ensuring patient-subjects provide a fully informed consent when they enroll in research trials," she tells *IRB Advisor*. "Informed consent is about respecting people's autonomy. If people are making decisions based on biases and errors in judgment, then there is a harm."

Cancer patients desperate to fight the disease may perceive participation in an early-phase cancer trial as an option by which they can assume some control over the course of the disease, she explains in a recently published paper.[1] These perceptions of control can in turn evoke "optimistic bias:" erroneous thinking that exaggerates the likelihood of benefit.

For example, in a Phase I cancer trial designed to test the toxicity of drugs, research subjects may be informed that participating will not benefit their health. The trial could, however, generate data that may be beneficial to future patients. Despite this relatively straightforward informed consent, some subjects in such trials manifest optimistic bias, she says.

"Even though that information is in the documents and hopefully included in the informed consent discussion between the researcher and the patient, when you interview patients they have this view that they are going to benefit from these trials," Jansen says. "That's the reason they are enrolling: to cure their cancer. And they have the belief that they are more likely to benefit than other people who are in the same trial. So something is happening in between the IRB approving the informed consent — which provides specific, concrete information that this trial is not designed to benefit you — and the time when the person agrees to participate and actually enrolls. There's a disconnect."

Beyond positive thinking

Jansen and other researchers have previously identified therapeutic optimism as a possible defect in the process of informed consent of early-phase cancer research.[2] Certainly, some research subjects will reflect a positive attitude indicative of the way they cope with life, but optimistic bias suggests a failure to adequately process or appreciate relevant research information.

"Beyond the concern for autonomy there is also an issue of well-being," she says. "We don't know how a person who enrolls in an early phase cancer trial is going to feel at the end of that trial when it does not improve their condition — if they are thinking that it will. So there is potential harm to a person's well-being and autonomy, and I think both of those are ethical issues."

As a practical matter, Jansen suggests the researchers specifically ask research patients their perceptions of the benefits of the clinical trial rather than simply telling them and giving them a form to sign.

"Step one is for researchers to be aware that there is this perception of control and this optimistic bias and one is generating the other," she says. "When they are having the conversation of informed consent, ask the question: 'What do you think your chances are of benefiting from this trial?' If those chances are exaggerated, then take a moment to reclarify what the chances are."

Similarly, researchers can ask research subjects their thoughts on their degree of control of the trial outcome. "If the person says they have a high degree of control over experiencing a health benefit, then the researcher can re-educate them about the nature of the research," Jansen says.

Psych factors

Jansen argues that these perceptions of control may trigger optimistic bias, citing a study that found that 44% of subjects in a cancer trial said that participating gave them a sense of control over their disease. They concluded that the "desire to actively do something to fight their cancer appears to motivate these participants to enroll in Phase I oncology trials."[3] Again, this sense

of control was often accompanied by a belief that they would benefit personally from the trial, while many other participants would not. This is strongly indicative of the optimistic bias, she says.

"Everyone cares about informed consent, but it's more than giving a form to a person," she says. "There is a psychology that people bring with them in that context. Researchers and IRBs need to be aware of that psychology and once we are aware of psychological [factors] that undermine risk-benefit processing — and even just understanding the information we are providing — then we can start talking about more concrete interventions that IRBs and researchers can engage in to improve how people process the information."

In that regard, Jansen suggests an area that holds promise to resolve the situation is "mindset" research. In other fields of study, an illusory and exaggerated sense of control has been linked to a specific mindset associated with implementation of adopted plans or goals. The "implementation mindset" occurs when a decision has been made to act. Though additional research would be needed to verify the hypothesis, Jansen says early-phase cancer trial research patients appear to manifest the implementation mindset.

Having decided to participate in an early-phase cancer trial, research subjects take action and by implementing their plan have an increased perception of control and, subsequently, optimistic bias about their health outcome, she says. Jansen theorizes that the aforementioned "disconnect" is because research subjects may not be in the implementation mindset when they first agree to the informed consent. The theory awaits more research, and Jansen is also interested in determining if optimistic bias can be found in later-stage cancer trials.

"We've only studied the optimistic bias in the context of early phase cancer trials," she says. "We are looking at later-stage trials and trying to determine if the bias still exists."

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BEST PRACTICES *SPOTLIGHT*

Next stage for IRB collaborations: Better communication and connections

A connected IRB model can work

It's complicated for research organizations to operationalize oversight of studies when relying on a single IRB for review of a multisite study, and the Notice of Proposed Rulemaking (NPRM) might even complicate things more. The proposed rule would mandate the use of a single IRB that all institutions involved in cooperative research would rely on, and it would make the IRB of record responsible for compliance.

Whether or not the NPRM changes are realized, the key to success with a centralized IRB approach is communication, says **Kimberly Irvine**, executive vice president and chief operating officer at Biomedical Research Alliance of New York (BRANY) in Lake Success.

An IRB of record should have a model that focuses on immediate and thorough communication, connecting research stakeholders seamlessly, Irvine says. "Oversight is one of the challenges institutions will be grappling with in coming years."

BRANY was formed in 1998 by academic medical centers with the goal of bringing more efficiency to the clinical trial process, she says.

"It had gotten to be a very long and laborious process to get industry-sponsored clinical trials up and running," Irvine says. "The medical centers that formed BRANY decided they could centralize some of these requirements, like the IRB review and budget negotiation, to make the process more efficient."

In the 18 years since its founding, BRANY has customized the process to make it easier for institutions to have oversight and to stay connected

to research projects, she notes.

The result is a connected IRB process that keeps all parties well informed about each review step and action.

The following is how it works:

• **The process relies on embedded notifications.** The system has embedded notifications that send automatic alerts. The alerts might simply say that a particular physician has submitted a study for review, giving the doctor's medical center an opportunity for oversight, Irvine says.

"They have an opportunity to put a hold on something if they want to," she says. "This enhances the organization's ability to oversee everything, and it will be more and more relevant as we see organizations utilize other IRBs under [rules by] the NPRM."

There are a variety of embedded notifications in the forms and electronic system, all designed to help institutions manage their programs and to help them feel connected to the process, Irvine says.

For instance, the notices began immediately. "Notices are sent out prior to a study being submitted to the committee for review," Irvine says. "It's a simple, basic notice, saying the study will be presented at the IRB meeting on this date; here's the principal investigator and the protocol title."

Another notification example involves an institution's pharmacy. Some organizations want an embedded notification that will send the pharmacy information about new studies, Irvine says.

• **Screening makes sure all pre-review actions are completed.** "The system asks investigators if they have gone through their internal committees," Irvine says. "We're following institutions' requirements."

Participating institutions can see at any time the status of research projects, she adds.

"If there are internal review committees, training requirements, or conflict of interest parameters for the organization, we can screen for that," Irvine says. "If we understand what's required, then we can build in screening for those things, and if an investigator has not met the threshold, an alert goes off."

> "IT HAD GOTTEN TO BE A VERY LONG AND LABORIOUS PROCESS TO GET INDUSTRY-SPONSORED CLINICAL TRIALS UP AND RUNNING."

• **Direct electronic access to IRB decisions is helpful.** If someone at a research institution would like more information about an IRB's decision regarding a particular protocol, they can log into the system and directly access the information, Irvine says.

The electronic list includes all active studies and, additionally, monthly reports, which give institutions easy access to the information, she says.

"Sometimes an institution will say to us, 'We want to know whenever you get a Phase I study, so a system to notify institutional representatives can be built around this parameter,'" Irvine explains.

• **Connected IRB model enhances local control.** "One of the things organizations struggle with when they think about outsourcing is the feeling they'll lose control," Irvine says.

They worry they won't know what's going on with studies within their organization and that they'll lose control of research under their authority, she adds.

Ever since BRANY was founded, it was offered as an option for IRBs — not a mandate. "Organizations can use their internal IRB or rely on the BRANY IRB," Irvine says. "Each institution is different, and they've made certain rules within their organization about when an independent IRB can be utilized."

As organizations now refine the way they have oversight of their research, one way to facilitate better management by institutions is to have a connected relationship with outside providers, she adds.

Better communication is the key, so if there is anything out of the ordinary that occurs, it will be communicated to the institution, and the two organizations will stay involved, Irvine says.

The connected IRB model provides immediate access to records, detailed reports, and ready contact with the BRANY IRB when institutions or researchers have questions, she says.

• **Reports also enhance engagement.** "A list of ongoing active studies with BRANY are provided to institutions' liaisons on a monthly or quarterly basis, whichever is decided," she says.

Adverse events also are communicated electronically to liaisons, which helps reduce some of the burden on principal investigators, she notes.

"Sometimes institutions have a duplicated reporting process where the investigator is required to report to the local IRB and to the

IRB of record for the study," Irvine says. "In our model, we've reduced the redundancy because we're reporting back to the institution, so the investigator doesn't have to do all of the reporting."

One of the chief aspects of a connected IRB model is to operate the IRB of record in a way that reflects what relying institutions need, including implementing some operational and procedural processes that help them better manage their research in their institutions, Irvine says.

"By adding some of these unique processes that were specific to the institution gives them more confidence and improves the way they can manage research within their organization," she adds. "We use information we receive to benefit all parties in the institution." ■

Ethics tool could enhance protocols and subject protection

Idea is to give IRBs more information

Too often, IRBs review protocols that make scant mention of ethical questions and issues. If anything, these sections of a protocol are limited to standard language, which does not suggest that researchers have given ethics a thorough consideration. A multiple stakeholder group seeks to change this with a novel project involving a protocol ethics tool kit.

"There is almost always an ethics section in industry protocols, but it tends to be a boilerplate: 'We'll follow good clinical practice and IRB requirements and get consent from the legally authorized representative,'" says **David Forster**, JD, MA, CIP, chief compliance officer with WIRB-Copernicus Group of Princeton, NJ. Forster is one of 20 authors involved in a paper published about the tool kit.[1]

"We propose they go through all the issues we put into the tool and address them one by one," Forster says. "It'd be a more robust and fact-based section."

The ethics tool kit covers 11 essential elements, providing for each one a short explanation, specific points to consider, background information, practical examples, and references.[1]

While the ethics tool kit was designed to be used by investigators, it contains information that IRBs can use to make sure there is no missing information regarding ethics considerations in protocols, says **Lindsay McNair**, MD, MPH, MSB, chief medical officer and president of consulting services at WIRB-Copernicus Group. McNair is the physician editor for *IRB Advisor*.

"It's a guide to what you have to think about and need included in the protocol," McNair says.

Forster and McNair provide this information about the 11 essential elements that should be included in protocols:

1. Addressing the relevant question. "This item is sometimes addressed well and sometimes not addressed at all," Forster says.

It's about why the research is important and the knowledge gap that's being addressed.

"It's partly about the issue of the study's design," Forster says. "Maybe the study has been done and proven, and there is no need to put people at risk."

2. Choice of control and standard of care. "This is one of the more important elements," Forster says.

Sponsors make decisions about control regimens in light of existing standard of care. There can be a brilliantly designed protocol that puts people at risk, he adds. "What's going to happen to potential subjects if they're enrolled?"

For instance, certain placebo designs and wash-out periods can be too risky to ask people to participate in, he says.

"What we get in protocols is a description of the study design, but we never get a background statement of why this study design is OK," Forster says. "And you need to look at the available standard of care; if a researcher's doing a study in sub-Saharan Africa, there is a very different standard of care when compared with the studies done in the U.S."

These kinds of issues can be addressed in protocols.

3. Choice of study design. "Usually there are a lot of discussions when a protocol is written about what is scientifically appropriate to do," McNair says. "When researchers write a protocol, they write the conclusion and don't show the work it took to get to that answer."

When IRBs receive the given conclusion, they typically do not see the underlying decisions, explanations, and justifications, she adds. "These can answer a lot of the questions an IRB would have."

Some larger academic research centers might have a separate study design review committee, but often there isn't one, Forster notes.

The 11 essential elements were designed for all research settings, including those used in countries where there is a weak research structure, McNair says.

4. Choice of subject population. "This element is about using a population that could be considered vulnerable or selected for reasons of convenience," McNair says.

Researchers need to say why they're using that population for the study. For instance, if a researcher chooses to enroll prison inmates, is it because the study needs this particular population, or is it because they are convenient and largely willing to participate, she says.

Some of the past research abuses occurred because investigators chose to study vulnerable populations based on their convenience, Forster says.

"There is the Willowbrook study, which took place at a state institution for mentally disabled children," he says.

At Willowbrook State School in Staten Island, NY, the mentally disabled children housed there had a 30% to 50% risk of contracting hepatitis A, according to the National Institutes of Health (NIH). *(For more information on the study, visit http://1.usa.gov/1RCG5mu.)*

Researchers in the 1950s enrolled more than 700 Willowbrook children in a hepatitis study that included injecting protective antibodies into one group and withholding protection from the control group, and observing the children's degree of immunity to hepatitis. But research ethicists point to how the study crossed ethical lines by deliberately infecting some newly admitted children with the hepatitis virus, the NIH paper says.

A more recent example of selecting subject populations based on convenience is when investigators do research in a location where no one has access to health insurance or care, so they enroll in the study to receive care, McNair notes.

> "WE PROPOSE THEY GO THROUGH ALL THE ISSUES WE PUT INTO THE TOOL AND ADDRESS THEM ONE BY ONE ... IT'D BE A MORE ROBUST AND FACT-BASED [ETHICS] SECTION."

5. Potential benefits and harms. "Sponsors clearly go through the thought process of minimizing risk, but all we're left with at the IRB level is their conclusions," Forster says. "The conclusion is embedded in the protocol, but we get no discussion about why a particular dose is acceptable risk or how benefits to community or subjects will be realized."

6. Informed consent. "Usually, the protocol says we will obtain informed consent with good clinical practice," Forster says.

But protocols say nothing about how participants' capacity to provide informed consent could change over the course of study enrollment, he says.

For example, a study that enrolls patients with mild Alzheimer's disease has subjects who may progress to dementia over a study's three-year period, Forster explains.

It would be helpful to have sponsors think through this issue and include in the protocol specific actions that will ensure subjects maintain the capacity to provide consent, he adds.

7. Community engagement. This essential element is specific to research in developing countries and underserved communities in developed countries, McNair says.

"It's about community engagement," she says.

The idea also is to ensure that researchers consider the ethical implications of conducting research within a low-resource community and what it means to use that community and then take off as soon as the study is complete, McNair adds.

Community engagement means that researchers should have plans to meet with the community and be sensitive to a marginalized and socially sensitive community's issues, Forster says.

8. Return of research results and incidental findings. This issue has become the focus of a working group of the Multi-Regional Clinical Trials Center (MRCT), which was involved in creating the protocol ethics tool kit, McNair notes.

The MRCT is developing detailed recommendations about what should be done after a study is over. "If you find things you didn't expect, do you give the information to [professionals] who know what to do with it?" she says.

Research participants often want to know the findings of a study, so

investigators could at least include information in the protocol about whether this information will be provided to them. They also could include information about how incidental findings are handled and whether participants have the ability to opt in or opt out of receiving incidental findings.[1]

9. Post-trial access. "It's not that you have to give people access to a study drug after the study is over, but you need to have a plan before the study is over," McNair says.

"Currently, protocols are silent on this issue," Forster says.

Researchers should address the question of whether there is a plan in the protocol about providing post-trial access to medications, McNair says.

10. Payment for participation. "It's the standard in the industry to not address this as part of the protocol and to leave it up to each site," Forster says.

Although sponsors often include this information in the informed consent document, it also should be in the protocol, he adds.

"How much will you pay subjects to recruit them?" he says. "We might get a brief description, but no rationale, and we want them to say, 'We'll pay this amount because it's a strain on their time or life.'"

11. Study-related injury. "This last essential element often is taken care of, but it's just not included in the protocol," Forster says. "Different countries have different requirements regarding insurance for clinical studies."

Some nations require study participants to get insurance that will cover study-related injuries, for instance. "We want IRBs to see a full disclosure about this," Forster says.

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Here's how to improve reviews of socio-behavioral protocols

Adverse reactions can be delayed

IRBs that predominantly review biomedical protocols might find it less clear in determining risks when reviewing socio-behavioral research.

"Risk is much less obvious and clear-cut," says **Jeffrey Cohen**, PhD, senior advisor at HRP Consulting Group in Lake Success, NY.

In working with IRBs since the late 1970s, Cohen has found that IRBs often misunderstand the concept of risk in socio-behavioral research. "In biomedical research, you have an intervention, certain side effects, and the biomedical risks usually are much clearer," he says.

"With socio-behavioral research risks, while there's rarely any possibility of physical harm, we're talking about possible social and psychological harms that are not always obvious," Cohen adds. "The implications for subjects are more subtle, more difficult to establish, and that presents a problem."

Cohen offers the following example: "Years ago, at a university, we had a study where the researcher was going to interview subjects about normal child development," he recalls. "The researcher was not going to ask about any kind of past trauma or abuse, so the study was considered minimal risk and received an expedited review from the IRB."

The researcher began to enroll subjects, and, suddenly, an unexpected problem arose: Three of the first five subjects had acute emotional breakdowns.

"So we stopped the study and sent the questions he was asking to a child psychologist," Cohen says. "The psychologist said, 'The way you've worded the questions would trigger an emotional reaction in someone who had a traumatic experience as a child.'"

With that expert advice, the researcher reworded the questions and included a sentence in the informed consent telling potential participants that if they have had a traumatic experience as a child, then they might not want to be in the study, Cohen says.

"We never had another problem," he adds.

This example highlights how subjective potential socio-behavioral harm can be. The investigator and IRB members lacked child psychology expertise and personal childhood experience with trauma; the study's questions appeared innocuous to them, Cohen explains.

"That leads to another issue about unanticipated problems in social and behavioral research," he adds.

"Researchers have to be alert to what's going on and how subjects are reacting to a study and know what to do if there is a problem."

They might not be able to anticipate how people will react, but they can have a plan in place to help participants when something in a study does cause an adverse reaction.

Also, IRBs and researchers should keep in mind that adverse reactions to socio-behavioral studies might not occur immediately after the intervention as you would expect in biomedical research, Cohen says.

"Psychological and social implications can be delayed; they don't happen right away," Cohen says. "Psychological effects are subtle."

The potential for a delayed reaction makes it especially important that the informed consent process emphasizes who a subject can call if he or she is experiencing a problem as a result of the study. The names and numbers listed on the informed consent form might also include a counselor's contact information, Cohen says. "It might say, 'After the study's over, if you are having concerns about being in the study, then here's who you should call.'"

It's also difficult to anticipate and outline potential adverse effects in the informed consent form because some risks are ones that only the study participant can evaluate, he says.

"The informed consent should empower the subjects and give them enough information so they can decide for themselves what the risks are," Cohen says. "One person could look at a given study and say, 'This is fine.' Another person could look at the same study and say, 'I don't want to be in this study.'"

When principal investigators submit a socio-behavioral protocol to the IRB, they should address the literature and what it has to say about risks involving similar types of studies, and IRBs should consider literature findings as well, Cohen suggests.

"They need to go back to evidence-based decision-making," he says.

For example, in the 1980s, a number of studies focused on depression inventories, and IRBs sometimes would say that researchers couldn't ask study subjects about suicidal ideation or those kinds of questions because it might push people over the edge, Cohen explains.

"But there has been quite a lot of research done that shows that not only did that problem not happen, that asking about suicide did not increase the risk, but that it was even beneficial," he adds. "So our IRBs now would say about one of those studies, 'OK, we're not concerned about this.'"

Also, IRBs should pay close attention to the study's subject population, Cohen advises.

"Risk is very much dependent on individual subjects, social situations, and psychological situations, so IRBs often need more information about who the subjects are going to be," he explains. "Instead of just saying it will be 10 males and 10 females or 'I'm interviewing college students,' IRBs will need to probe more into who the subjects are before making a determination about how they'll react."

According to Cohen, the following are three chief points to keep in mind when reviewing a socio-behavioral study:

- **Don't assume you know what will trigger a reaction.**
- **Have a process ready to handle unanticipated reactions, including calling the principal investigator.**
- **Be aware that reactions can occur weeks or months later.**

"This is about an IRB's need to recognize that social and behavioral risks are not as obvious as medical risks, and so they should take care," Cohen says. "Don't overreact, but really look closely at the possibilities." ■

AMA calls for clinical trial transparency

Influential physician group joins AllTrials campaign

The American Medical Association (AMA) has joined the AllTrials initiative, giving the campaign for clinical trial data transparency a formidable ally with the largest physician membership in the U.S.

"The AMA joining AllTrials represents an incredible step forward for clinical trial transparency, and the U.S. arm of this initiative," says **Lauren Quattrochi**, PhD, director of AllTrials USA.

The AMA's support shows that the issue of clinical trial transparency is vitally important for practicing physicians and the integrity of medicine, she tells *IRB Advisor*.

"Doctors need all the information when they are making treatment decisions for their patients, and this is impossible if the data on current medications are compromised by the failure to register trials and

report results," says Quattrochi, who directs the initiative as a project of Sense About Science, based in Brooklyn, NY. "We can work toward accomplishing this level of transparency if those involved in making the daily, patient-tailored treatment decisions are well-informed."

The AMA's Medical Student Section called for enhanced clinical trial transparency and support of the AllTrials initiative at the association's 2015 Interim House of Delegates meeting. The delegates adopted a policy during the meeting to support the timely dissemination of clinical trial data, improved enforcement deadlines for sharing these results, and expanded registration for clinical trials to improve clinical practice and policy. After getting the green light from its board of trustees, the AMA recently joined the AllTrials initiative.

"The AMA strongly supports improving the timeliness and accessibility of clinical trial data to reduce the duplication of research and help inform future research — ultimately improving health outcomes for patients," AMA President **Steven J. Stack**, MD, said in a statement.

Founded in the U.K., the AllTrials campaign — a varied group of patient advocates, medical associations, and academia — brought their crusade for clinical trial transparency to the United States in July 2015. They argue that many clinical trials, involving hundreds of thousands of patients, have never reported results. AllTrials calls for all past and present clinical trials to be registered and their full methods and summary results reported.

"In the U.S., we are keen to build on the evident enthusiasm among medical students for trial transparency," Quattrochi says. "Medical students are our next generation of doctors, and their expertise will help move their respective fields forward — but not unless they have the data they need to make appropriate decisions. By focusing their attention on this issue now, we believe these doctors will help build a more transparent future for medicine."

No excuse

In addition to a total blackout of trial results, another concern is that data that shows efficacy or benefit in one portion of a clinical trial may be revealed independently. AllTrials is not seeking regulation or government mandates for clinical trial data disclosure. Instead, the group has adopted a strategy of activism, historical inevitably, and coercion that urges the medical industry to get on board.

"There is no excuse for clinical trials not to be registered and their results reported in a timely manner," Quattrochi says. "Clinical trial participants would benefit from their data [being] accessible. Even if the trial does not alleviate or cure their ailment, the outcome may help others down the road."

Withholding trial data from physicians could also contribute to needless duplication in research with little medical benefit.

"Moreover, how do we as researchers know that we haven't missed an opportunity to explore a novel therapy or discover a new application for a drug if previous work has been kept unpublished?" she says.

AMA joins 641 patient advocacy groups, professional societies, medical organizations, and thousands of patients worldwide in supporting the global AllTrials campaign.

"We have barely scratched the surface for what is possible," Quattrochi says. "America is just one country where clinical trial data has been left on the cutting room floor. We aim to expand into every major country and assist their medical, research, and patient communities into building a better infrastructure to capture and responsibly share data."

AMA joins other U.S. physician-based groups that have endorsed AllTrials, including the American College of Physicians and the American Academy of Family Physicians.

"Our next step here in the U.S. is to continue to build a dialogue around clinical trial transparency among patient advocacy groups, scientific societies, academic institutions, and pharmaceutical researchers," she says. "We can collectively act as a catalyst for a cultural shift that will promote all trial results to be shared for the greater good." ■

COMING IN FUTURE MONTHS

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IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. According to Lynn A. Jansen, PhD, optimistic bias in early-phase cancer patients may undermine which of the following?

A. Informed consent
B. Patient autonomy
C. Patient well-being
D. All of the above

2. Which of the following items is not one of the essential elements of the protocol ethics tool kit created by a group that included the Multi-Regional Clinical Trials Center (MRCT)?

A. Choice of control and standard of care.
B. Choice of study design.
C. Choice of clinical trial monitor.
D. Choice of subject population.

3. According to Jeffrey Cohen, PhD, which of the following are chief points to keep in mind when reviewing a socio-behavioral study?

A. Don't assume you know what will trigger a reaction; have a process ready to handle unanticipated reactions, and be aware that reactions can occur weeks or months later.
B. All socio-behavioral studies should be minimal to no risk; expedited review should be the default action.
C. Socio-behavioral studies involving personal questions need to have a full board review; don't assume any particular question is innocuous.
D. All of the above.

4. Which section of the American Medical Association's membership prompted a call for transparency that led to joining the AllTrials campaign?

A. Resident and fellow
B. Integrated physician practice
C. Women physicians
D. Medical student

IRB Advisor

2016 Reader Survey

In an effort to learn more about the professionals who read *IRB Advisor*, we are conducting this reader survey. The results will be used to enhance the content and format of this publication.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Fax the completed questionnaire to 678-974-5419, return it in the enclosed postage-paid envelope, or complete online at https://www.surveymonkey.com/r/IRB_Advisor_survey. The deadline is **July 1, 2016**.

1. How would you describe your satisfaction with your subscription to *IRB Advisor* newsletter?

   O A. very satisfied O B. somewhat satisfied O C. somewhat dissatisfied O D. very dissatisfied

2. Are the articles in *IRB Advisor* newsletter written about issues of importance and concern to you?

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Questions 3-10 ask about the importance of various topics in *IRB Advisor* newsletter. Please fill in your answer using the key below.

	A. very important	**B. fairly important**	**C. not very important**	**D. not at all important**
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5. subject recruitment	O A	O B	O C	O D
6. ethical conflicts	O A	O B	O C	O D
7. office best practices	O A	O B	O C	O D
8. subject compensation	O A	O B	O C	O D
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10. HIPAA	O A	O B	O C	O D

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12. article selections	O A	O B	O C	O D
13. timeliness	O A	O B	O C	O D
14. length of newsletter	O A	O B	O C	O D
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16. customer service	O A	O B	O C	O D

17. Do you plan to renew your subscription to *IRB Advisor*?

    O A. yes O A. no

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18. What can *IRB Advisor* do to improve?_____

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20. How many IRBs does your institution sponsor?

O A. 1 O B. 2 O C. 3 O D. 4 O E. 5-10 O F. 11 or more

21. How many studies does your IRB oversee each year?

O A. 1-5 O B. 6-10 O C. 11-15 O D. 16-25 O E. more than 25 per year

22. How would you categorize your IRB?

O A. affiliated with a university
O B. independent consultants
O C. affiliated with a Department of Health
O D. Other_____

23. In what capacity do you serve on the board?

O A. coordinator O B. chair O C. co-chair
O D. scientist O E. community member (non scientist) O F. other_____

24. To what other publications or information sources do you subscribe?_____

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25. Which publications or information source do you find most useful?_____

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