IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

AUGUST 2017 Vol. 17, No. 8; p. 85-96

INSIDE

AHC Media
A RELIAS LEARNING COMPANY

ICMJE Underlines Ethics on Importance of Data Sharing

Tamiflu is a case in point

By Melinda Young, Author

When IRB members and research ethicists consider the debate over sharing clinical trial data with the public and other researchers, there is one example they might wish to consider: Oseltamivir, known as Tamiflu.

Tamiflu, which was designed to treat influenza symptoms, was widely stockpiled by governments around the world more than a decade ago. Out of concern of a worldwide pandemic flu, they wanted something in their arsenals to help slow the spread of the disease and help alleviate discomfort in those infected.

Published studies suggested the benefits of the drug outweighed the expense and patient side effects. Scientific skeptics challenged those conclusions and spent several years pushing Tamiflu's manufacturer, Roche, to release Tamiflu trials data.

> THE COCHRANE COLLABORATION PUBLISHED RESULTS OF A REVIEW OF THE UNPUBLISHED TRIAL DATA, SHOWING IT HAD NO EFFECT ON HOSPITALIZATIONS OR SECONDARY INFECTIONS, SUCH AS PNEUMONIA.

The Cochrane Collaboration published results of a review of the unpublished trial data, showing that although the drug shortened flu-like illness by less than a day, it had no effect on hospitalizations or secondary infections, such as pneumonia.[1]

"There seems to be marginal evidence of its effectiveness," says **Mark Schreiner**, MD, executive vice-chair of the committee for protection of human subjects (CPHS) at the Children's Hospital of Philadelphia (CHOP).

Financial Disclosure: Author **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Editor **Dana Spector**, AHC Media Editorial Group Manager **Terrey L. Hatcher**, Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics, and Nurse Planner **Kay Ball**, RN, PhD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

IRB ADVISOR

IRB Advisor,
ISSN 1535-2064, is published monthly by
AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.
GST Registration Number: R128870672.

POSTMASTER: Send address changes to:
IRB Advisor
P.O. Box 74008694
Chicago, IL 60674-8694

SUBSCRIBER INFORMATION:
Customer Service: (800) 688-2421.
Customer.Service@AHCMedia.com.
AHCMedia.com

SUBSCRIPTION PRICES:
Subscription rates: U.S.A., Print: 1 year (12 issues) with free AMA Category 1 CreditsTM or Nursing Contact Hours, $419. Add $19.99 for shipping & handling. Online only, single user: 1 year with free AMA Category 1 CreditsTM or Nursing Contact Hours, $369. Outside U.S., add $30 per year, total prepaid in U.S. funds.

MULTIPLE COPIES: Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

ACCREDITATION: Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias Learning designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias Learning, LLC, is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [1.5] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

This activity is intended for clinical trial research physicians and nurses. It is in effect for 36 months from the date of publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

AUTHOR: Melinda Young
MEDICAL WRITER: Gary Evans
EDITOR: Jill Drachenberg
EDITOR: Dana Spector
AHC MEDIA EDITORIAL GROUP MANAGER: Terrey L. Hatcher
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger

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

In Europe, governments spent billions of dollars to stockpile a drug of questionable value, Schreiner says.

Greater clinical trial data transparency could prevent costly mistakes, and it's something that already is provided for pediatric research through provisions in the Best Pharmaceuticals for Children Act, he adds.

"The pediatrics act requires study reports," he says. "You can find information online about lots of studies that failed because they were mandated to be there since the early 2000s, and that's the level of transparency that is missing in most drugs developed first for adults."

The International Committee of Medical Journal Editors (ICMJE) published an editorial in June 2017, saying there is an ethical obligation to share interventional clinical trial data.[2]

Beginning July 1, 2018, manuscripts with clinical trial results that are submitted to ICMJE journals must contain a data-sharing statement.[2]

Data-sharing statements must include the following[2]:

- Will individual de-identified participant data be shared?
- What data will be shared?
- Are related documents available, such as study protocol and statistical analysis plan?
- When, and for how long, will data become available?
- What access criteria data will be shared, and by whom?[2]

"What ICMJE is about is not just sharing data so it can be used, but it's about increasing the transparency in the process so that everybody can learn from what's been done," Schreiner says.

It's also about maximizing the utility of the data from clinical trials.

"To maximize societal benefits from the sacrifice or willingness of volunteers to take part in clinical trials, we should make data available at some point in time so other investigators can explore or use this for other purposes," Schreiner explains.

This cooperative approach might be good for society, but some people in the research community fear it could allow someone else to swoop in and benefit from their hard work.

For instance, suppose a drug trial failed for its intended indication. But a data analysis reveals that some participants have a genetic variant that led to a positive response, says **Barbara Engel**, MD, PhD, CPHS chair at CHOP.

"So you do another trial, focusing on people with those variants," Engel says. "With some justification, researchers might worry that someone else will get hold of this data and do this trial before they get a chance to."

The ICMJE's perspective is that if society is going to fund research and volunteers are willing to take risks to benefit society, then potential gains from the research should be maximized, Schreiner notes.

"In an ideal world, this is a cooperative venture between people who understand data and people who ask the question, and I'd hope this would be a partnership rather than marauders swooping in," he says.

IRBs and those who work in human research protection need to make sure risks and benefits are appropriate when reviewing studies, but they do not have a defined role for follow-up studies that use de-identified data.

"It's our expectation researchers will use this data, and it may

inform future research, but how it's specifically defined is not always known going into the initial review," says **Amy Schwarzhoff**, MBA, CIP, director of human subjects research at CHOP.

However, IRBs can ensure that study sponsors intend to publish results.

"We ask people to discuss their plans for publication," Schreiner says. "We have, in fact, deferred studies from pharmaceutical companies that say they own data and no one will be able to publish it."

Sponsors sometimes do this because they don't want to give away their secrets until there's a confirmatory study, he adds. "People have novel ideas, and they believe if details come out, someone could scoop them."

But what can happen is that one company runs a clinical trial in a new class of drugs. The study fails and is not published. Then another company has a similar agent in the same new class, runs the study, and it also fails and is not published. By the time a fifth clinical trial is begun in the same class of failed agents, hundreds of people have volunteered their time and risked their health. And the latest people to enroll have no way of knowing that every other trial of that class of drugs has failed, Schreiner explains.

"We always joked there should be a journal of failed experiments," Engel says. "If failed clinical trials were published, we might learn from these." ■

REFERENCES

1. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews*. 2014;4. http://bit.ly/2sUJci1.
2. Taichman DB, Sahni P, Pinborg A, et al. *Annals Int Med*. June 6, 2017, editorial:1-3.

Assent Is Not Consent: Children in Clinical Trials Are Not Little Adults

Engaging children in research decisions has positive effects

The classic admonition in pediatric medicine is "children are not little adults," implying in part that you cannot just scale down adult care and treatment. Does this phrase resonate as well in human research trials involving children, particularly around issues of consent for the former and assent for the latter?

"Yes, I think that many of the practices that we have related to assent [in children] come from the adult model of consent, which is problematic for several reasons," says **Victoria A. Miller**, PhD, director of research in the Division of Adolescent Medicine at the Children's Hospital of Philadelphia (CHOP). "Kids are a moving target in terms of developmental changes — cognitively, but also emotionally and psychosocially. They have varying levels of experience with decision-making generally, and certainly in terms of whether they have participated in research or not, how familiar they are with the medical environment, and, specifically, health-related decision-making. They are learning how to make decisions."

Miller is researching ways to empower children in this process, though ultimately, their parents must agree to participation in a clinical trial as part of relational decision process involving both parties.

"I think that the assent process is really an opportunity for them to practice" making decisions, she tells *IRB Advisor*. "And also, I would apply this to adults as well. Kids are not alone in a vacuum. They want parental input. They need parental input in decision-making. Other studies have shown that they do want the parents' guidance. The focus on autonomy and competence can really detract from this idea that decision-making is really a relational process and there are multiple individuals involved. There are many ways the kids can and should be involved in the decision."

Delving into this concept, Miller and colleagues conducted a study[1] to analyze children's involvement in decisions about research participation, including their perceptions of the decision-making process and "self-efficacy." Children, ages 8 to 17 years, who were enrolled in research studies in the previous two months were asked to complete a questionnaire with their parents' involvement that centered on three decision-making types:

• researcher engages child;
• researcher supports autonomy;
• child participates.

The study was approved by the CHOP IRB. After obtaining parental permission and child assent, research staff administered the questionnaires separately to parents and children by phone or in person if the family preferred.

Higher scores on the researcher-engages-child category were associated with greater self-efficacy in children, and higher scores on the researcher-supports-autonomy type were associated with greater perceived fairness by kids.

"These data underscore the potential importance of researcher–child interactions about research participation when assent is sought, including proactively involving children in the decision by asking for their opinions and communicating their central role in the decision, which are likely to be more meaningful to children than receiving information or signing a form," the authors concluded.

IRB Advisor asked Miller to elaborate on some of the findings.

IRB Advisor: You found higher scores with one approach correlated with greater self-efficacy, while another was perceived with high fairness. Can you comment on the implications of these findings for IRBs and researchers, respectively? Should studies that seek assent through these approaches be encouraged?

Miller: Yes, absolutely. I think because of using the adult model of consent as the model for [child] assent there has been too much focus on the assent form and disclosing certain bits of information and covering all of these different details about the proposed research that may or may not be important for kids to know. I can't make a blanket statement about what should or should not be included because I did not look at that specifically, but I think because of the focus on information disclosure we've neglected this idea of "how do we talk to kids?" So, yes, I think the findings support the idea that investigators and research staff should be encouraged to talk to children and ask their opinion:

I THINK THE FINDINGS SUPPORT THE IDEA THAT INVESTIGATORS AND RESEARCH STAFF SHOULD BE ENCOURAGED TO TALK TO CHILDREN AND ASK THEIR OPINION. THE ULTIMATE QUESTION IS, "DO YOU WANT TO DO THIS OR NOT?"

"What do you think? What are you concerned about?" The ultimate question is, "Do you want to do this or not?"

This is about really understanding where they are coming from and how they are thinking about the decision. I think it is important and beneficial to kids to have that kind of discussion and interchange, as opposed to, "Here are 10 bullet points on these different details about the study." Yes, that's important for parental permission, and it is important for adult informed consent, and it gets more important as the child gets older and more cognitively mature, and closer to the legal age of competence. But for many kids, most of that information is less important.

IRB Advisor: In a sense, could pursuit of these issues open a path to better assent or informed consent and ultimately improved protection and reduced risk to children participating in trials? Is there some perception or concern that children need these protections; i.e., that they and their parents may be assenting to inappropriate or higher-risk research than warranted?

Miller: No, not necessarily. That's not the assumption of my research. The IRB is tasked first of all with judging whether the risks are reasonable in relation to the benefits. And then parents as well are tasked with that for their individual child when they are asked to provide permission for the research. So, I think the idea of risk is less relevant when it comes to kids, although certainly enhancing the assent process gives kids an opportunity to express their own concerns about the procedures involved. For example, whether they are comfortable or not. Or whether participation [in the research] could be emotionally stressing in some way. Whether or not those meet the level of risk as we think of it from an IRB perspective, I think that's up for debate.

IRB Advisor: Can you elaborate on the meaning and impact of "self-efficacy" in concluding that, "when children perceived that researchers proactively engaged them by soliciting questions and asking for an opinion, children reported greater decision self-efficacy?"

Miller: Self-efficacy in general refers to competence in one's ability to perform certain actions that are needed to produce a desired result. There is self-efficacy for many different things; there is self-efficacy for losing weight or for managing type 1 diabetes.

In this context, I measured self-efficacy related to health decision-making. This study assessed things like, "How confident are you that you can understand what your parents or doctors are telling you? How confident are you that you can ask questions without feeling dumb? How confident are you that you can talk to your doctor about what worries you?" Those sorts of things. I think that is really important when we think about involving kids not only in research decisions, but all sorts of medical decisions. By sending the message, "You're opinion matters. We want to hear what you think. We're listening to you," that gives them confidence, hopefully, to play more of a role and be better able to make decisions in the future.

IRB Advisor: So you see ancillary benefits beyond just checking the box that assent was given?

Miller: There are certainly ethical and legal reasons to acquire assent for research participation, but I think the process of assent can benefit kids. It's like being in a lab and practicing, making these sorts of decisions and hearing how people talk about decision-making. Hearing that their voice does matter and that they can play a role — and should play a role — in that decision in some way.

IRB Advisor: Your findings also underscore that, among children who enroll in research studies, explicit communication that addresses the child's right to decline participation is associated with more favorable views of the decision-making process. While you note the conflict with parental permission, can you comment on why this "right to decline" is important in child research subjects?

Miller: I think in a medical environment, children aren't accustomed to being able to say, "no." Much of that happens because it has to happen; it is a clear benefit to their health. So, the right to decline is really unique here. I did find that it was associated with favorable views of decision-making, partly because kids are not used to hearing that. I think that they recognize and, hopefully, appreciate that they do have the choice about whether or not to participate. Obviously, you can't have assent without also having the right to decline. When you are asking children whether or not they would like to do this, the right to decline has to go with that.

IT JUST MIGHT BE THAT WHETHER THE CHILD IS ACTUALLY SPEAKING UP OR NOT, IT'S AGAIN THOSE MESSAGES AND BEHAVIORS FROM THE ADULTS THAT REALLY DRIVE CHILDREN'S PERCEPTIONS OF THE PROCESS.

IRB Advisor: Children's verbal participation in the assent discussion (e.g., expressing an opinion, asking questions) was not associated with perceptions of fairness or self-efficacy. That seems counterintuitive. Can you comment on what may have happened there?

Miller: I think there are a lot of potential reasons for that. As we mention in the paper, I'd say in both the research context and the clinical context children's verbal participation is low in these types of encounters and discussions. There is clearly a power differential. They are used to parents deciding in these situations and being the prime communicator. Parents do intervene with kids' verbal participation as well. There is research showing that the parents will jump in, interrupt, and answer questions that are directed to the child. Also, the kid may just lack the communication skills to speak up. There are adults, of course, that often don't participate a lot in medical encounters.

Another potential explanation is just that the questionnaire didn't really capture the children's verbal participation adequately. Although I have found [something similar] in another analysis that I am doing right now. Ultimately, it just might be that whether the child is actually speaking up or not, it's again those messages and behaviors from the adults that really drive children's perceptions of the process. ■

REFERENCE

1. Miller VA, Feudtner C, Jawad AF. Children's Decision-Making Involvement About Research Participation: Associations With Perceived Fairness and Self-Efficacy. *J Empir Res Hum Res Ethics*. 2017 Apr;12(2):87-96.

FDA's Draft Guidance on eRecords Could Have Unintended Consequences

The FDA's draft guidance on the use of electronic records and electronic signatures encourages electronic systems to improve quality and efficiency of clinical investigations.[1]

The draft guidance, published June 20, 2017, also expands the use of a risk-based approach in validating and establishing audit trails for electronic systems.[1]

It's the validation part of the proposed guidance that could introduce a new problem. The draft says that "sponsors and other regulated entities should have electronic systems validated if those systems process critical records (e.g., records containing laboratory and study endpoint data, information on serious adverse events and study participant deaths, information on drug and device accountability and administration) that are submitted to the FDA."

"It puts responsibility on sponsors," says **Raymond Nomizu**, JD, co-founder of Clinical Research IO of Cambridge, MA.

"As a software vendor, I do worry about proposing regulatory liability on sponsors and whether it will make them unwilling to innovate," Nomizu says. "On one hand, the FDA is encouraging use of electronic systems and integration across systems. But they're imposing regulatory liability on the sponsors to ensure that the systems and the integrations are validated and working appropriately."

This creates a disincentive for integration, he adds.

"You can't really have it both ways," Nomizu says. "I don't think the FDA is fully sensitive to how much of a stultifying impact their words can have."

For instance, if a technology vendor has a new offering that could be an improvement, the sponsor has a disincentive to switch from its existing electronic system because of the need to validate the change, he says.

While liability for electronic technology should be the vendors' responsibility, the FDA does not have jurisdiction over vendors, which is likely why the proposed guidance was written this way, Nomizu says.

Research institutions also might have responsibility for validating their electronic systems, but doing this could be complicated, says **Susan Rose**, PhD, executive director of the office for the protection of research subjects at the University of Southern California in Los Angeles.

"The goals of the guidance is to expand the risk-based approach, data trails, and archiving of records," Rose says.

The guidance says that electronic records should be archived in a way that records can be searched, sorted, or analyzed and have the same capacity as other records when inspected by the FDA.[1]

This will be a cost that studies need to anticipate, Rose says. "Studies need to save enough money to store data after studies are done."

The FDA's guidance also says that processes should be in place to control electronic system changes and to evaluate whether and how much to revalidate with changes. It reads, "When changes are made to the electronic system (e.g., system and software upgrades, including security and performance patches, equipment or component replacement, or new instrumentation), sponsors and other regulated entities should evaluate the effect of the changes and validate the changes using a risk-based approach."[1]

The guidance adds that major changes "may require additional revalidation and critical changes could trigger a revalidation of the entire system."

The FDA will focus on implementation of electronic systems and changes made to the system during inspections. And the FDA recommends sponsors and other regulated entities perform periodic audits, conducted by trusted third parties, of the vendor's electronic systems and products.[1]

Validation also is necessary when mobile technology is used in clinical investigations. The FDA states, "Validation ensures that the mobile technology is reliably capturing, transmitting, and recording data to produce accurate, reliable, and complete records. For example, if a wearable biosensor detects a blood glucose level of 87 milligrams per deciliter, the validation should ensure that the value is correctly and reliably captured, transmitted, and recorded in the sponsor's EDC system."[1]

In some ways, the FDA's guidance is just acknowledging the reality of an electronic future, Rose notes.

"People were doing a lot of [work electronically], but were questioning whether or not it would be okay, so now clinical trials — depending on the intervention — could do a huge amount of the trial electronically," she says. ■

Small IRB Revises Forms, Updates Policies and Procedures to Obtain FWA and Reach Next Level

When leaders at a small, private teaching college decided to shift their focus to more research, they hired a research director who could make that happen.

"When I came on board, we had an IRB, but it didn't meet the requirements for the federal standards and Common Rule of the Federalwide Assurance [FWA]," says **Megan Roth**, PhD, director of research and sponsored programs and IRB chair at Abilene Christian University (ACU) in Texas.

"A new focus of the institution was to broaden research and do more grant seeking, and we wanted to revamp the entire focus to set up a system that was able and capable of receiving those funds," Roth says. "When I came in, I had to look at the system and determine what wasn't meeting those standards and what changes I needed to implement to take it to that level where we could apply and receive federal funding."

Roth took the following steps to remake the human research protection program (HRPP) at the university:

• **Identify problems.** Soon after beginning work as the director of research, Roth reviewed existing processes and forms.

"I spent a month or two working within the existing system and trying to get a feel for how it was working and to identify areas that were problematic," she says.

Then Roth read through federal regulations, meticulously noting all requirements and rules and outlining which of these were missing from the IRB's existing policies and procedures.

"I had a notebook that outlined everything we needed to do to take it to that next level," Roth says.

• **Update forms and create new ones.** The institution's existing form was general, without specific questions.

"One of the problems was there was great variability in how much detail was provided on the form," Roth says. "Some protocols that came in were very good and some were grossly lacking in information needed to make an assessment."

> "TOO MUCH REVIEW IS BETTER THAN NOT ENOUGH, BUT IT CREATES AN UNNECESSARY BURDEN ON EVERYONE INVOLVED WHEN STUDIES ARE BEING IMPROPERLY ROUTED."

This resulted in forms being sent back and forth multiple times, which frustrated researchers. ACU also had no clear process for determining exempt reviews versus full board, she says.

"A lot of studies were being over-reviewed," Roth says. "Too much review is better than not enough, but it creates an unnecessary burden on everyone involved when studies are being improperly routed."

Roth created all new forms. Since the IRB does not have an electronic platform, all forms were created for paper.

"I looked at a lot of forms from different institutions," she says. "I combed through the regulations and looked at the key things that needed to be assessed."

Roth looked for forms on other IRBs' websites, but also participated in listservs and boards and asked research administrators for help.

"Research administrators are very, very generous, and we rely heavily on each other to not reinvent the wheel," she says. "You can say, 'Does anybody have a policy you wouldn't mind sharing with me?' and most folks are very happy to let you use what they have."

Within a few months, Roth rolled out the new forms, which include forms for vulnerable populations, consent templates, and waiver of consent. ACU also implemented a process for properly routing everything and determining whether an effort involved human subjects research or was exempt.

• **Train IRB members on changes.** The IRB has 11 members and the support of one part-time administrative assistant. The administrative assistant receives the same training as the IRB members, Roth says.

Before the rollout of the new IRB system, Roth provided board members with a day of training on the forms and changes.

"I walked them through it and made sure they understood everything and had read through

all the regulations before we had that meeting," Roth says. "I helped them make the connection between regulations and the forms and what they are supposed to be assessing when they ask questions."

Roth also showed IRB members how the new forms would make it easier for them to assess protocols and reduce the number of times a protocol needed to be sent back to the researcher for more information.

"There was a lot of back and forth that would drag out the approval process for a long time," she says. "These new forms are more efficient because they get to the meat and potatoes of what you need to know to make your decision."

IRB members recognized the need for a better system, so most of the changes were well received, she notes.

Other than a couple of situations where some board members disagreed with a decision, discussions showed they were open to changes. "Some had experience with IRBs at other institutions and knew we had to make some changes," Roth says.

• **Roll out the new system.** Roth came on board in June 2015, and ACU rolled out the new system Oct. 1, 2015. She revamped all forms and the IRB's website, which now has a page explaining every step in the IRB process, including:

- submitting an application;
- amending an active study;
- obtaining a continuing review;
- reporting a problem;
- meeting training requirements.

The website now includes a section of frequently asked questions and a forms database, where people can search for any form they might need.

Part of the rollout included Roth giving presentations on campus for faculty, showing them how the research submission process worked and what they might expect if they conducted a human subjects research project.

"For faculty, going from a short, vague form to a much longer system with many more questions and documents was a little bit daunting," Roth says. "It was helpful for me to show them the specific meaning behind the questions."

Roth showed faculty the new forms during her presentations and went through each process step by step.

"I talked about what the regulations require and how these questions tied into those things," she says. "It really hits on the key points of the Belmont Report."

This helps people connect the policies with regulations and the ethical basis behind both.

For example, a researcher might wonder why the study's demographics need to be reported. Roth would help link that question to the Belmont Report, showing that the real intent is research ethics.

"We're asking for very specific things that will help their protocol go through faster," Roth says.

Several rollout talks took place at the faculty development center for faculty and deans. Others were given to student groups, targeting students who would be conducting summer research projects.

"The first year, I did six to eight different talks around campus to bring awareness to the changes," Roth says.

Researchers' reactions were similar to IRB members with most of them liking the change and appreciative of an improved IRB process, she says.

• **Apply for FWA.** Taking all of the notes she'd made from reading through the human research protection regulations, Roth wrote the policies and procedures (P&Ps) necessary to apply for FWA.

The 30-page P&P manual for FWA also serves as the IRB handbook. Because Roth already had written new forms, FAQs, and revised the website, much of the writing she needed for the P&Ps was already done, she says.

The main remaining work was to place the policy work into an organized narrative form. The handbook contains the following features:

- statement of principles;
- IRB organization and composition;
- information on running IRB meetings;
- procedures for initial review, continuing review, amendments;
- handling noncompliance problems;
- policies for record storage;
- handling classroom projects and quality improvement projects;
- handling external requests with people not affiliated with the institution, and dealing with additional topics.

The institution received the FWA and is ready to apply for federal funding for human subjects research, Roth says. "I feel like we have a system to manage that and apply for those studies."

• **Revise P&Ps as necessary.** With the new Common Rule changes now expected to go into effect in 2018, Roth plans to revise the P&Ps to reflect those changes.

"I'm going to need to make some revisions to the forms and questions that we ask," she says. "I started combing through the revisions in the spring, and my hope is to finish doing that this summer."

Roth will review the changes, assess how they will affect the IRB processes, and make revisions reflecting those changes.

"Then, I'd like to get the changes rolled out in the fall of this year," Roth adds. ■

Gray Zone Remains Between Clinical Research and Quality Improvement Efforts

With no resolution by HHS, calls for a non-IRB alternative

The boundary between quality improvement (QI) projects and clinical research requiring IRB oversight remains nebulous with finalization of the Common Rule on Jan. 18, 2017. There was some attempt to address this situation in the proposed new rule, but ultimately the solutions were deemed problematic and the issue was left unresolved, explains **Joshua Rolnick**, MD, JD, a clinical scholar in the National Clinician Scholars Program at the University of Pennsylvania.

Among the proposed changes in the Notice of Proposed Rulemaking (NPRM) were an exclusion for QI activities and interventions designed to change an accepted practice. The exclusion reflected a desire to create a new framework that addressed the need for QI intervention in a "learning healthcare system." As noted, the final rule discarded the proposal, and Rolnick and colleagues agreed with that particular move in a recent analysis. However, the overall problem remains.

"We believe that HHS was correct to reject in the final rule the proposed QI exclusion in the NPRM, which provided a flawed attempt to distinguish QI from research," they concluded.[1] "However, the final rule carries forward the problems of the original Common Rule for oversight of QI activities. First, uncertainty regarding the need for IRB review discourages careful efforts to understand the impact of individual QI efforts, exerting a chilling effect on the conduct and publication of QI evaluation, when ethical oversight of QI should result in incentives to improve healthcare delivery. Second, reliance on the Common Rule creates an inverse relationship between methodological rigor and oversight: systematic evaluation of QI interventions receives the administrative oversight of the IRB, while less systematic QI efforts are usually subject to little or no ethical review."

"WE BELIEVE THAT HHS WAS CORRECT TO REJECT IN THE FINAL RULE THE PROPOSED QI EXCLUSION IN THE NPRM, WHICH PROVIDED A FLAWED ATTEMPT TO DISTINGUISH QI FROM RESEARCH."

This conclusion would certainly suggest that hospitals may be tempted to dilute the rigor of a QI project rather than risk facing the scrutiny of IRB review.

"I think that temptation does exist," Rolnick says. "To be fair, there are many excellent QI practitioners using innovative methods to evaluate interventions in a rigorous fashion without employing the traditional techniques of clinical research. And sometimes practitioners will decide to use a technique like randomization, fold the evaluation under the umbrella of clinical research, and go through the usual IRB channels. However, I think that uncertainty about IRB status and the implications of classifying an evaluation as clinical research does discourage the use of techniques like randomization when they might be appropriate."

Generally speaking, a hospital trying to improve compliance with hand hygiene or implement a sepsis prevention protocol as QI projects might approach the realm of clinical research if, for example, patients who receive intervention and those who do not are randomized.

"The use of randomization is often treated as an indication that the evaluation should be considered research rather than quality improvement, although specific practices vary by institution," Rolnick says. "However, randomizing by design should be distinguished from the kind of pseudorandomization that sometimes occurs through institutional practice. Interventions are often used first in certain units for a host of operational reasons, which can sometimes create a sort of pseudorandomization. This is less likely to be regarded as an indicator that the evaluation is clinical research."

Rolnick and colleagues strongly question whether this randomization threshold between QI and clinical research is appropriate.

"We question if this reasoning makes sense, on either legal or ethical grounds," says Rolnick, who is both a physician and an attorney. "On legal grounds, the implicit case is that randomization makes the results more generalizable to other medical settings. However, it is not clear that this is usually the case. Randomizations may improve the ability to tease out cause and effect — i.e., internal validity. However, whether randomization improves external validity is a different question. In fact, sometimes randomization involves the use of protocols that depart from routine clinical care, making results more difficult to generalize than those from a purely observational evaluation."

On ethical grounds, it is unclear why using randomization to determine if a patient receives an intervention has a different ethical status from the myriad nonclinical factors that can influence who receives an intervention, he adds.

"Staffing considerations, for example, may determine whether an intervention is piloted in one ward or three," he notes.

To address this issue, Rolnick proposes locating ethical oversight of QI outside the IRB system, in a different locus that better connects quality improvement with clinical practice. This approach, at the onset, would recognize the close connection between QI and clinical care. One option is creating a separate "QI-IRB" to address ethical issues specifically raised by QI as distinct from clinical research, he says.

"I think that separate panels for QI would enable hospitals to better embed ethical oversight of QI in operations, thus allowing smoother integration with the other aspects of overseeing a new QI intervention," he says. "For example, many QI interventions now involve the electronic health record, and many EHR systems offer randomization capabilities. Clinical informatics is well poised to offer oversight. It's already establishing itself as a distinct area of practice. Many institutions have informatics committees, and clinical informatics has its own fellowship training and board certifications. These committees may have the experience and capacity to take on this oversight function alongside operational oversight of EHR interventions."

Even with QI-IRBs in place, Rolnick and colleagues warn that the "problems of consent and the inverse relationship between methodological rigor and oversight still apply. A better system would be one operating outside the IRB framework and, thus, designed more flexibly to accommodate the unique features of QI. Is such a system possible without regulatory reform? To a degree, we believe only better federal rules would bring clarity."

In the interim, clinical decision support (CDS) committees also could help overcome obstacles to improving care and patient outcomes.

"I think clinical decision support committees could offer guidance to practitioners on when IRB oversight is required, how to navigate that process, and how to ensure ethical practice when the IRB is not involved," he says. "I would also like CDS committees to encourage rigorous evaluation of interventions. They might nudge practitioners to use techniques like randomization when suitable, and help liaise with the IRB to determine the best form of ethical oversight for a given case. Part of that, in my opinion, would include noting when randomization may not necessarily prompt the need for IRB review."

In any case, it goes without saying that healthcare systems have an ethical obligation to conduct QI efforts in the name of patient safety and improved outcomes. Regardless of IRB oversight, ethical principles apply to QI projects, including the following basic tenets summarized from a study cited by Rolnick.[2]

- **Social or scientific value:** Benefit should justify resources and risks.
- **Scientific validity:** Grounded in science and appropriately designed.
- **Fair subject selection:** Burdens and benefits should be fairly distributed.
- **Favorable risk-benefit ratio:** Protocol should emphasize minimal risk and maximum benefit.
- **Respect for participants:** Protect privacy and confidentiality. Inform participants of clinically relevant findings.
- **Informed consent:** Patients should give "background consent" to minimal risk QI as part of agreement for treatment.
- **Independent review:** Accountability should be a requisite feature of QI. Ethical review should match the level of risk and project benefit. ■

REFERENCES

1. Rolnick J, Downing NL, Shieh L, et al. Ethical Oversight of Quality Improvement and the Research-QI Boundary: A New Common Rule Changes Little. *IRB: Ethics & Human Research* 2017;39(3):1-10.
2. Baily MA, Bottrell M, Lynn J, et al. The Ethics of Using QI Methods to Improve Health Care Quality and Safety. *Hasting Center Special Report* 2006;36:(4):S1-S40.

Very Strict Clinical Trial Criteria Can Pose Ethical Problem

Clinical trials routinely use overly strict enrollment criteria, found a recent study.[1] "Real-world patients are often excluded from clinical trials because they do not meet the restrictive eligibility criteria," says lead author **Abby Statler**, MPH, MA, research regulatory quality assurance coordinator for the leukemia program in the Department of Hematology and Medical Oncology at Cleveland (OH) Clinic.

Researchers studied the relationship between eligibility criteria and adverse events in randomized controlled trials of hematologic malignancies. "We wanted to understand if there are specific criteria that may be responsible for inappropriately excluding patients," Statler explains.

The results suggest that excluding patients with hepatic, renal, or cardiac abnormalities may not be justified, given the safety profiles of the study interventions. Of the 97 randomized controlled trials analyzed, 21% had the potential to cause nephrotoxicity. But nearly 74% of the trials excluded patients with renal abnormalities.

"The results relevant to neurological function did not follow this same trajectory," says Statler. "Our findings indicate exclusion of patients with peripheral neuropathy may not be conservative enough."

Statler adds, "Our findings suggest clinical research may unintentionally evoke a health equity dilemma."

Clinical trials are designed to contribute to society's general knowledge regarding the diagnosis, cure, mitigation, treatment, or prevention of disease. The study's findings suggest that the studies' results are only applicable to a select cohort of patients. "These select groups of potential beneficiaries are essentially established by the respective clinical trials' eligibility criteria," says Statler.

Many commonly used exclusion criteria may not be appropriate, given the study interventions' safety profiles. Thus, widespread use might lead to the exclusion of specific groups of patients. "Furthermore, because cancer is a life-threatening disease, access to novel therapies is essential," Statler says.

Overly restrictive criteria may limit the therapy options for specific patient populations, such as people with organ function abnormalities or comorbidities. "This presents ethical issues related to justice," says Statler. ■

REFERENCE

1. Statler A, Radivoyevitch T, Siebenaller C, et al. The relationship between eligibility criteria and adverse events in randomized controlled trials of hematologic malignancies. *Leukemia* (7 December 2016) doi:10.1038/leu.2016.374

Paper Calls for More Transparency of Industry-sponsored Clinical Trials

A recent paper offers consensus recommendations and examples of best practices from the published clinical trial literature to help authors and trial sponsors communicate drug adverse events in a more informative and clinically meaningful manner.[1]

"The intent of the paper is to help improve the reporting of safety outcomes from clinical trials," says **Jesse Berlin**, senior vice president and global head of epidemiology at Johnson & Johnson in Titusville, NJ. Overall increased transparency is the overarching goal.

"Improving safety reporting is just one part of the broader emphasis across the research community on improving transparency with respect to our data," says Berlin. Recent initiatives have focused on sharing both summary and participant-level data from clinical trials.

"Disclosure of all results — both favorable and unfavorable — is a visible demonstration that industry is reporting the benefits and the risks," says Berlin.

The complete data set is then made available for those interested in performing further analyses. "Increased transparency is an ethical obligation we have to the people and care providers who have participated in studies, and those who use our products," Berlin says. ■

REFERENCE

1. Lineberry N, Berlin JA, Mansi B, et al. Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective. *BMJ* 2016; 355;i5078.

IRB ADVISOR

CME/CE INSTRUCTIONS

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

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

CME/CE QUESTIONS

1. **The International Committee of Medical Journal Editors (ICMJE) published an editorial in June 2017, saying there is an ethical obligation to share interventional clinical trial data. Which of the following is not a statement ICMJE says must be included in data-sharing statements?**

   a. Will individual de-identified participant data be shared?
   b. Will data be published on the World Health Organization website?
   c. Are related documents available, such as study protocol, statistical analysis plan?
   d. What access criteria data will be shared and by whom?

2. **In a study of child research subjects, which of the following approaches was associated with a perception of greater "fairness" by the children?**

   a. Researcher engages child
   b. Researcher supports autonomy
   c. Child participates
   d. All of the above

3. **The FDA's draft guidance, published June 21, 2017, on the use of electronic records and electronic signatures encourages electronic systems to improve quality and efficiency of clinical investigations. It also does which of the following?**

   a. It expands the use of a risk-based approach in validating and establishing audit trails for electronic systems.
   b. It suggests research institutions should have full responsibility for all electronic systems used in clinical trials — whether or not these are owned by the institution or researcher.
   c. It outlines how electronic systems are superior to paper processes in protecting confidential subject information.
   d. None of the above

4. **Which of the following often is considered an indication that a QI project should be considered research that is subject to IRB approval?**

   a. When more than one clinical unit is involved
   b. When one patient population is more vulnerable than a control group
   c. When the intervention is randomized
   d. All of the above