IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

JULY 2019 Vol. 19, No. 7; p. 73-84

INSIDE

RELIAS MEDIA

The RAC Is Disappearing — What Will IRBs Be Missing?

Change eliminates a layer of review

By Melinda Young

In the two decades since Jesse Gelsinger died during a gene therapy clinical trial in September 1999, the clinical trial industry has treated gene therapy studies with additional caution.

Until now.

The balance is changing. The National Institutes of Health (NIH) is eliminating the Recombinant DNA Advisory Committee (RAC). After Gelsinger's death, RAC was given enhanced oversight authority to improve checks and balances in research subject safety. *(More information can be found at: https://go.nature.com/2tK5SlQ.)*

Now, NIH has published new guidelines to streamline gene transfer research by eliminating RAC's pre-review role and closing a national database of gene transfer studies. Titled *Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, the notice was published on April 26, 2019. *(The guidance is available at: http://bit.ly/2Z0ROSX.)*

> "GENE TRANSFER, OR WHAT IS CALLED GENE ADDITION NOW, DOESN'T CREATE ENOUGH NOVELTY TO SUSTAIN THE RAC. BUT GENE EDITING HAS CHANGED THE LANDSCAPE."

These new guidelines for gene therapy research put more responsibility on IRBs for assessing gene transfer studies' safety and have elicited 43 public comments — both for and against the changes. *(The comments can be found at: http://bit.ly/2T4JnaO.)*

The guidelines also eliminate pre-review at the federal level of any protocol for biosafety before new studies go to local biosafety committees, says **Daniel Kavanagh**, PhD, senior

Financial Disclosure: Author **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Editor **Jesse Saffron**, Editorial Group Manager **Leslie Coplin**, Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics, and Nurse Planner **Kay Ball**, PhD, RN, CNOR, CMLSO, FAAN, 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 Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *IRB Advisor*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.
GST Registration Number: R128870672.

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The prior process was for principal investigators at the first clinical trial site to submit an Appendix M response to the Office of Science Policy (OSP) at NIH. Then, the NIH director would decide whether to refer the protocol to RAC as a pre-review step before it landed on the desks of IRBs, he explains.

"Up until 2016, RAC would review every protocol before it went forward," Kavanagh adds. "All were registered in the federal database and sent back to the local institutional biosafety committee [IBC] for approval."

Now, RAC is gone, and in its place is the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC). The new entity will not review protocols, leaving that role to research sites' ethics boards. *(See story on how IRBs will need to change, page 75.)*

The rationale for the change is that gene therapy studies are no longer novel and in need of additional oversight, notes **Nancy M.P. King**, JD, professor in the department of social sciences and health policy at Wake Forest School of Medicine in Winston-Salem, NC. King also is the co-director of the Center for Bioethics, Health, and Society and graduate program in bioethics.

"Gene transfer, or what is called gene addition now, doesn't create enough novelty to sustain the RAC," King says. "But gene editing has changed the landscape."

King, a former RAC member, submitted a comment to NIH that opposed the change that would eliminate RAC's authority.

"IBCs and IRBs still need guidance when reviewing gene transfer research protocols," King wrote in her comment to NIH. "Simply ditching Appendix M might not be the best way to proceed."

One of the underlying problems is that IBCs need more support than they receive, King says.

"IBCs have a very broad institutional mandate, and gene addition is only one small part of it," she adds.

Whether IRBs and IBCs can handle the responsibility of reviewing gene transfer protocols without RAC's help remains to be seen, she says.

"They probably are fine with gene addition research, but with all of this new genetic research, everybody needs more assistance," King says. "NExTRAC is pretty far removed from advising IBCs."

Many organizations and individuals commenting on the new NIH guidance said they were pleased to see NIH streamline oversight of gene transfer clinical research protocols and reduce duplication in reporting requirements.

For instance, the Immune Deficiency Foundation (IDF) submitted comments that applauded the change: "As the NIH and FDA noted in issuing this proposal, while such intense and overlapping oversight had its place, much has changed in recent years to justify a change that reduces regulatory burdens while still ensuring research participants are protected."

NIH's replacement of RAC with NExTRAC is the right change at the right time, says **Donald B. Kohn**, MD, distinguished professor of microbiology, immunology, molecular genetics and pediatrics, and molecular and medical pharmacology at the University of California, Los Angeles (UCLA).

Kohn assisted IDF with writing the comments for NIH.

"I think it is time to eliminate the RAC reviewing every gene therapy protocol, as the FDA and local IRBs can monitor quality, safety concerns, etc.," Kohn says. "But the RAC plays an important role as an open public forum to discuss issues of novel biosafety concerns, as it did when recombinant DNA technologies were first being developed."

Another important change is that the Genetic Modification Clinical Research Information System (GeMCRIS) database will be eliminated.

"The database is going away," Kavanagh says. "NIH stopped updating it last August with action by the NIH director, and by the fall of 2019, it will be taken offline."

The result will be the loss of data that are valuable to some researchers and experts in the gene transfer research community.

"There are only a few of us specialists who found that database useful, and we will have downloaded everything before they take it offline," Kavanagh says. "Everyone who cares has a copy on their computer, but it is a loss of information."

Although research trials are listed on ClinicalTrials.gov, that database does not have as much information as did GeMCRIS, Kohn says.

"It is important to keep a complete registry of the numbers of patients getting various gene therapies while it is still an emerging treatment," Kohn says.

With publicly-listed patient numbers, regulators and watchdog groups will know how many people could be impacted by safety issues and risks, he adds.

The premise behind the elimination of GeMCRIS is that gene therapy protocols are not different enough from other clinical research to justify having their own database, Kavanagh explains.

But there is risk: "Some gene transfer protocols are very high-risk in terms of potential harm to subjects, and some of them are moderate-risk in terms of potential harm to the public," Kavanagh says.

"The IBC is mostly focused on

How IRBs Can Fill in the RAC Gap

With changes to how gene therapy research is reviewed and regulated, IRBs will need to do more on their own to ensure study participant safety.

The *Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* eliminates the Recombinant DNA Advisory Committee (RAC) and its pre-review of gene transfer trials. It also closes a national database of these studies, and stops study subject reviews by local institutional biosafety committees (IBCs).

The changes mean that IRBs must be prepared to assess risks and benefits of gene therapy studies without the benefit of a RAC review and an IBC review.

Here is what IRBs and IBCs can do to fill the gap:

• **Collaborate.** "With the RAC being removed from the picture, essentially, IRBs and IBCs need to work together on this," says **Nancy M.P. King**, JD, professor in the department of social sciences and health policy at Wake Forest School of Medicine in Winston-Salem, NC. King also is the co-director of the Center for Bioethics, Health, and Society and graduate program in bioethics.

IRBs should think of IBCs as consulting specialists. When an IRB receives a gene therapy protocol, the IRB office could call the IBC and ask for its opinion on the study's safety and proceed from there, King suggests.

• **Network.** IRBs lack a good mechanism for talking to each other about new types of studies, King says.

"They go to the PRIM&R meetings and have informal networks with other IRBs, but there is no mechanism for formal coordination. That's a general problem with any potentially controversial or risky research," King explains. "What you want is an opportunity to talk together about those studies."

IRB members and directors should develop relationships with their peers so they can contact them when a new question or need arises, she says.

• **Seek experts.** Before the NIH's changes to gene transfer research regulation, there were multiple eyes looking at each protocol, says **Daniel Kavanagh**, PhD, senior scientific advisor, gene therapy, WIRB-Copernicus Group (WCG) of Madison, WI.

"First, there was the federal level with the RAC, and then the IBC and IRB would look at it from a patient safety perspective," he says. "Now, there's just one set of eyes, which is the IRB, for subject safety."

Ideally, IRBs will have gene therapy research experts on the board or available to consult with the board. They also could seek expert advice when they receive a gene transfer study protocol, Kavanagh adds.

For instance, WCG has strong gene transfer research expertise and frequently consults with the IBC, he says. ■

whether there is risk the gene transfer agent will escape biocontainment and cause potential harm to people working in the clinic or in the general environment," he adds. "IBCs also, until April 2019, had an overlapping responsibility with the IRB."

Before the NIH changes, IBCs also assessed risk to clinical trial participants of gene transfer trials. They often had more gene therapy expertise on their committees, so IRBs benefited from their oversight.

"The FDA and NIH have decided that most IRBs have enough expertise available to assess these clinical trials without IBC assistance, in terms of risk to subjects," Kavanagh says.

IRBs that review gene therapy studies will need access to expert advice, and they might not be able to rely on their institutions' IBCs, as they have previously. IBCs still will review these studies, but solely for the purpose of determining occupational and public health risks.

"The IBC still reviews every protocol and still must issue an approval at every clinical trial site, but they're not assessing risks to subjects," Kavanagh explains. "They're assessing risk to everyone else — to the clinical staff, the general public, and to the environment."

The overlap of IBCs and IRBs assessing risk to subjects is gone. The change is in line with the Trump administration's stated goals of reducing regulations.

"I have not seen public information that the change is tied into a larger regulatory strategy of the administration, but it is a response to feelings by clinical trials sponsors that there was too much duplicative oversight," Kavanagh says. "Gene transfer work required more paperwork than other trials because of the large Appendix M document, and people trying to get their clinical trials started felt overly burdened."

Some biosafety committees filed comments with NIH, saying the change was a step too far, Kavanagh adds.

While a number of comments to the NIH changes supported them, some individuals also expressed concern that oversight of gene therapy studies would be more lax and dangerous going forward.

For instance, Jesse Gelsinger's father, Paul Gelsinger, wrote a comment to NIH about the change, asking the agency to not let history repeat itself.

"The death of innocence is something that we all must carry, and is an almost overwhelming burden," Gelsinger wrote. "Everybody failed Jesse Gelsinger at every level, and all he wanted to do was help." ■

How Can IRBs Best Handle Ethical Conflicts in Social Media Research?

IRBs often review protocols in which investigators are using social media as a recruitment tool or a way to inform study participants about a particular disease. They might also use social media to keep tabs on potential or current research subjects.

All of these intersections in the use of social media and human research protection can raise ethical red flags.

"There are so many ways to use social media in research, and each of these ways brings up a different ethical concern," says **Tamiko Eto**, MS, CIP, human research protection program (HRPP) manager at SRI International in Menlo Park, CA.

Here are some questions IRBs should be asking and resolving when working with protocols that engage with participants through social media:

• Is it acceptable to create a potential subject fan base?

Some researchers could use social media to set up a page that, essentially, creates a fan base for that site and its information, Eto says.

"People would 'like' the site and follow it, and by following it, they expose themselves and all of their information to the owner of that site," she adds.

An IRB's questions might include:

- Is it ethically OK to entice people to a social media site without disclosing that their information might result in a request to participate in a study?

- Is it acceptable to engage followers on social media, encouraging them to comment and participate when the primary goal is research and not disseminating information?

- What type of disclosure is acceptable when asking people to "like" or follow a research social media site?

"Sometimes, researchers do identify the site as for research, and sometimes they don't," Eto says. "That's why it's extremely important for IRBs to say, 'Give me the link.'"

When IRBs check out a

researcher's social media site, they can see if people are commenting and disclosing personal and private information that suggests they believe the site is a private forum when it is not, she adds.

"Someone could comment, 'I had an episode with my herpes last night,' thinking they are in a herpes support group," Eto offers as an example.

What investigators should do is set up these social media pages in a way that no one else can post information. It should be available simply to obtain information, she adds.

• Should investigators be allowed to pull publicly available Facebook profiles of potential subjects?

Website information and research study recruitment is very different from providing information and recruiting subjects on Facebook or Instagram. Depending on how investigators handle the social media messages, it could be intrusive or acceptable.

"In most cases, when they use that site as a source of recruitment, saying, for example, 'We're studying sleep disorders in menopausal women, and if you're interested, go to this website or call us,' it seems benign," Eto says.

But for some studies, such as research into illicit drug use, this can be risky, she adds.

When people engage with a social media page, their every "follow" or "like" identifies them as part of that community, she explains.

Also, it is possible for researchers to visit the homepages of people they encounter on social media and learn more about them from their public profiles.

"If researchers want to develop this group of a certain type of people, then what kind of settings does an IRB want them to have to protect certain [subject] information?" Eto says.

• What is the dividing line between social media ethical concerns and subject safety ethical concerns?

"This is where IRBs have to put on their IRB hats and say, 'These are social media ethical concerns, and these are human subjects research concerns,'" Eto says. "If it doesn't involve human subjects research, we can't touch it."

Some studies that use social media do not meet the criteria of human subjects research, and IRBs should not be concerned with those, she adds.

The way to tell the difference is to ask investigators these questions:

- What data are they pulling from the social media sites?
- How and with whom will the information be shared?
- Have investigators looked over the institution's policies regarding use of social media and research, and will they abide by those policies?

"There are multiple ways in which people want to use Facebook for research," Eto says.

"We have a policy for our institution that is not unique," she adds. "It includes asking for the links, reviewing those, and confirming that investigators know the rules and are abiding by the rules on each social media platform." ■

Into the Void: A Staggering Sum of Unreported Research Data

A call for ethics and action on 'academic misconduct'

By Gary Evans, Medical Writer

In what amounts to a stunning compromise of research principles, a recent review of clinical trials over a five-year period found that results were never published for almost 90,000 participants.[1]

The authors of the study — who could not be reached for comment — looked at large, unpublished clinical trials on ClinicalTrials.gov from 2007 to 2012. The researchers found 67 unreported trials with a median enrollment of 765 people. The numbers ranged from 511 to 11,000 research participants, resulting in a total of 87,883 people with unreported results for a median of nine years after the trial was completed.

"I think there needs to be some mechanism of follow-up on these studies. They are experiments on people — and not reporting [them] is academic misconduct," says **Harlan M. Krumholz**, MD, SM, director of the Center for Outcomes Research and Evaluation at Yale-New Haven (CT) Hospital.

Krumholz wrote an accompanying editorial[2] on the study along with

co-author **Joshua D. Wallach**, MS, PhD, an assistant professor of epidemiology at the Yale School of Public Health.

"When trial results are not made publicly available for years after study completion, patients, institutional review boards, clinicians, researchers, and the public must rely on incomplete evidence, which may lead to misconceptions about the efficacy and safety of interventions," Krumholz and Wallach wrote.

IRB Advisor asked Krumholz whether IRBs should emphasize publication in research oversight by, for example, making reporting of findings part of the informed consent process.

"Yes," he says. "For people not reporting results, future research studies should not be approved until the results are reported."

Not reporting research data "biases the medical literature and potentially leaves the wrong impression of what is true," Krumholz says. "It chills participant enthusiasm for research and betrays people's trust in the system."

The latter point is well taken considering the ongoing recruitment in the National Institutes of Health's All of Us trial, which had pushed transparency and research results as a major benefit of participation in trying to reach 1 million people.

In addition to the common perception that the results were not what the researchers were looking for, there currently is little consequence for not publishing findings, Wallach says.

"To the best of my knowledge, no fines have been issued based on violations of reporting requirements," he says. "For studies that are long unreported, there may be little incentive for authors to go back and share results."

Lost Data in Key Fields

Beyond the ethical principles, such findings raise the question of whether meaningful data on a variety of diseases is lost to subsequent investigators. The unpublished trials reported by Tatsioni et al included research on neurological diseases, cardiology, infections, psychiatrics, and women's health.[1]

"Without reported results and systematic reviews that can help guide practice and policy, we will not be able to evaluate and combine the results from all study sources," Wallach says. "Participants are likely to assume that the evidence that is generated from a clinical trial will help inform practice, which helps justify the individual risks that may be involved with signing up for a study."

The study by Tatsioni et al reinforces preceding evidence, suggesting unpublished research data is a longstanding problem. In particular, a previous study[3] looking at large trials prior to 2009 found even more research participants whose results were never reported, Wallach says.

"In that study, they focused on trials with at least 500 participants, finding that nearly 30% remained unpublished — with an estimated total enrollment of nearly 300,000 patients," he says. "This new study by Tatsioni et al focused on a more recent sample, and selected the largest studies that did not have results posted." ■

REFERENCES

1. Tatsioni A, Karassa FB, Goodman SN, et al. Letters: Lost Evidence From Registered Large Long-Unpublished Randomized Controlled Trials: A Survey. *Ann Intern Med* 2019 May 7.doi: 10.7326/M19-0440. [Epub ahead of print]
2. Wallach JD, Krumholz HM. Not Reporting Results of a Clinical Trial Is Academic Misconduct. *Ann Internal Med* 2019 May 7.doi: 10.7326/M19-1273. [Epub ahead of print]
3. Jones CW, Handler L, Crowell KE, et al. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ*. 2013 Oct 29;347:f6104.doi:10.1136/bmj.f6104.

NIH Urges Vigilance to Protect Research

Foreign agents targeted for theft of intellectual property

The FBI is continuing an investigation into "utterly unacceptable" foreign theft of and influence on research by the National Institutes of Health (NIH), said NIH Director **Francis Collins**, MD, PhD.

"We are deeply concerned about the evidence, which has been growing over the course of more than a year, that there are egregious instances where our funding of grants in this country is being taken advantage of by individuals who are not following the appropriate rules," Collins said in recent testimony to Congress. "This is utterly unacceptable. We have had multiple opportunities to interact with the FBI, which has been investigating this vigorously."

Collins sent a letter[1] last year to thousands of research institutions to be wary of research maleficence in three critical areas:

- Diversion of intellectual property in grant applications or from NIH biomedical research to other countries;
- Release of confidential information on grant applications by NIH peer reviewers to foreign entities;
- Failure by researchers at NIH-funded institutions to disclose resources from foreign governments.

Collins updated the situation in testimony at an April 11, 2019, hearing of the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies.

"We have uncovered what has led to 55 investigations ongoing of [researchers] who we believe may be double-dipping, receiving government money without disclosing it," he said. "Or, in some cases, diverting property they may be working [on] to China. … While China has been mentioned a lot, this is not only China."

In addition, and "maybe most egregiously of all," are those contributing to the theft by distributing research ideas when they are supposed to be performing peer review, he said. Collins told the committee that the message to NIH research institutions is "if they're not aware of what their own faculty are doing in terms of these kind of relationships, they need to begin to find out."

> THE MESSAGE TO NIH RESEARCH INSTITUTIONS IS "IF THEY'RE NOT AWARE OF WHAT THEIR OWN FACULTY ARE DOING IN TERMS OF THESE KIND OF RELATIONSHIPS, THEY NEED TO BEGIN TO FIND OUT."

After initially some surprise and "denial," institutions are beginning to take action, he said.

"There are instances where faculty have been fired, many of them returning to their previous foreign [countries]," Collins said. "Actions are being taken, and you'll see more evidence of that in the press."

Indeed, The University of Texas MD Anderson Cancer Center in Houston reportedly took action against some faculty members, but in a statement, it did not provide specifics.

"The institution has responded to requests from the NIH regarding a variety of threats, including data security and intellectual property loss," according to the statement.[2] "It's important to note that no patient information was accessed or shared."

The release included a statement by **Peter Pisters**, MD, president of MD Anderson, expressing the institution's commitment "to the highest levels of scientific integrity, public accountability, and social responsibility in the conduct of science."

Steps have been taken to safeguard the institution, including a new emphasis on risk management, increased awareness and education on data security, and strengthening of conflict of interest policies, MD Anderson reported.

"We have an obligation to do all we can to protect our intellectual property and all state and federal resources entrusted to us," Pisters said. ■

REFERENCE

1. Collins, F. NIH Foreign Influence Letter to Grantees. Aug. 20, 2018. Available at: https://bit.ly/2WDzrGV.
2. MD Anderson addresses national threat of foreign influence. April 19, 2019. Available at: https://bit.ly/2Wx2Cqe.

IRBs and Institutions Could Improve Monitoring Sites for Protocol Fidelity

When IRBs review multisite studies, particularly when the sites are at different research institutions — and in different states — there is a question about how faithfully each site sticks to the protocol and avoids deviations.

With large, multisite, non-biomedical studies, fidelity — or maintaining protocol compliance — requires considerable resources.

A new study found that when fidelity and other challenges are addressed, the study's scientific rigor and reproducibility are improved. It also found that multisite studies' findings are more likely to provide evidence that can transform clinical practice and policy.[1]

This fidelity to the protocol is something human research protection offices should monitor, experts say.

Fidelity is a concern, says **Laureen Smith**, PhD, RN, FAAN, associate professor at Ohio State University. Smith is a co-author of the study on multisite trials.

"If you have a trial going on in different states, then you have to build into your systems ways of monitoring that fidelity and who is responsible for that," Smith says.

"The challenge with having a single IRB of record is getting everyone on board to do the same thing," adds **Sonia A. Duffy**, PhD, RN, FAAN, Mildred E. Newton Endowed Chair at The Ohio State University College of Nursing.

IRBs might assume that everyone is following the protocol faithfully, but they cannot be certain of this unless there are procedures to check that every site is performing the protocol activities in precisely the same way.

"Everything has to be spelled out from the beginning so sites know exactly what they're signing up for," Smith says.

From the perspective of study participant safety, IRBs want to ensure everyone is being treated the same and that everyone is following the same protocol. Researchers have to tell the IRB who is responsible at each site for the protocol activities, Smith notes.

Multistate and multisite trials also pose other issues. For instance, investigators have to answer to each site's questions and rules, particularly with community-based research such as studies performed in schools, Smith says.

"I do community-based research, school-based research, and even though I have multiple sites and locations and one IRB of record, I still have to get the approval of each individual school district before conducting my study," she explains. "They have their own autonomy to say 'yes' or 'no.'"

One of Smith's most recent studies involved more than a dozen schools, and their concerns and questions varied. For instance, some schools only wanted to see a copy of the IRB's approval letter, and others wanted additional information. Some asked what kind of measures would be taken with the children and how invasive the work would be. They also questioned data collection, privacy measures, and confidentiality, she adds.

Researchers should be prepared for roadblocks to consistent protocol adherence due to varying state laws. The approved protocol should reflect those differences.

For example, Duffy was part of a smoking cessation study with sites across the country. Investigators ran into a barrier involving how to obtain data and informed consent of study participants with a specific comorbidity. States had different rules about how to access those data and what type of consent was required.

Researchers sometimes will need to drop a site because of state laws that make it difficult for the site to fully participate in the study and faithfully follow the protocol.

Duffy also conducted fidelity monitoring for a study that involved a nursing procedure with patients.

"I trained nurses in hospitals on how to make sure we are all doing the same thing," she says. "You go in and watch them work with the patient and follow a checklist about whether they covered medication and behavior, and you try to make sure people are all doing it the same way."

Fidelity monitoring is another layer of bureaucracy, and research institutions should be willing to negotiate and be as flexible as possible — but not flexible in a way that compromises the protocol, Duffy says.

"You need to figure out how you can work with the organization within their rules, and be open-minded to other options without compromising the study," she adds. ■

REFERENCE

1. Smith L, Tan A, Stephens JD, et al. Overcoming challenges in multisite trials. *Nurs Res*. 2019 May/Jun;68(3):227-236.doi:10.1097/NNR.0000000000000324.

Study Finds That All Financial Conflicts of Interest Influence Findings

New data fuel ethical worries on industry ties

All financial conflicts of interest (COI) influence whether study authors report findings favorable to industry sponsors, according to a recent investigation.[1]

"Historically, some industry-sponsored studies have had significant influence on the public, our patients, and our healthcare system," says **Karla Bernardi**, MD, one of the study's authors. When these studies were repeated by independent researchers, some findings were shown to be erroneous.

"In addition, there has been increased attention on individuals and institutions failing to fully disclose and manage their ties with industry," says Bernardi, a general surgery research fellow with McGovern Medical School at The University of Texas Health Science Center at Houston.

These well-publicized failures raised the question whether industry influenced the results reported by researchers. The investigators reviewed 590 research articles to determine whether authors who fail to disclose reportable COI are more likely to publish findings that are favorable to industry than authors with no COI. Two key findings:

- A 69% discordance rate existed between industry and self-report in COI disclosure;
- When authors failed to disclose COI, their findings were more likely to favor industry partners than authors without COI.

"Our team was surprised to find that any conflict of interest — relevant or not relevant, disclosed or undisclosed — will influence scientific reporting compared to studies with no financial conflict of interest," says Bernardi.

Need for Monetary Support

To conduct a well-structured trial, a researcher needs a substantial amount of capital. "Medical research has become more expensive over time. Unfortunately, there is not enough funding for all projects that individuals want to perform," says Bernardi.

> "THERE HAS BEEN INCREASED ATTENTION ON INDIVIDUALS AND INSTITUTIONS FAILING TO FULLY DISCLOSE AND MANAGE THEIR TIES WITH INDUSTRY."

Industry is a leading source of monetary support for possible advancements in medicine. "However, our study found that any conflict of interest affects the reporting of scientific studies," notes Bernardi.

For this reason, the researchers support the National Academy of Medicine (formerly the Institute of Medicine [IOM]) recommendation, she notes: "The IOM suggests that any individual with a conflict of interest should not be involved in human research."

The main ethical message from the study's findings, says **Matthew McCoy**, PhD, is that there is no such thing as a risk-free financial conflict. "Any kind of financial conflict has the potential to bias research," says McCoy.

It is possible that benefits associated with a particular financial conflict — for instance, funded research — might outweigh the risk of bias.

"But individuals and institutions need to acknowledge that there's always a tradeoff involved," says McCoy, an assistant professor in the department of medical ethics and health policy at the University of Pennsylvania's Perelman School of Medicine.

Disclosure Alone Does Not Neutralize

Given the potential for bias, it is important that all conflicts be disclosed so they can be evaluated. "But second, and more importantly, it's important to recognize that disclosure doesn't neutralize the risk of bias," says McCoy. It is a mistake to assume that just because a financial conflict is disclosed there is no reason to worry about it.

It is unclear to what extent, if any, research institutions will revise polices in the wake of increased scrutiny.

"But to the extent that institutions are taking this opportunity to review and revise COI polices, they ought to involve ethicists in the process," says McCoy.

One way to achieve this is to include ethicists on COI committees. Raising awareness also is an important ethics role, says McCoy.

"Ethicists can help to inform and educate the public about the importance of COI in medicine and what can be done to address them," he says. ■

REFERENCE

1. Cherla DV, Viso CP, Holihan JL, et al. The effect of financial conflict of interest, disclosure status, and relevance on medical research from the United States. *Gen Intern Med* 2019; 34(3):429-434.

Unique Informed Consent Challenges of Sequentially Randomized Trials

Repeat consent conversations are necessary sometimes

Elizabeth F. Krakow, MD, encountered some unexpected ethical challenges with informed consent after designing a sequentially randomized trial for patients with newly diagnosed acute myeloid leukemia.

The objective was to assess the utility and optimal timing of allogeneic stem cell transplantation compared to alternative treatment options.

"The treatments and timing of the treatments offered in the trial would depend on the disease response," explains Krakow, a researcher at Fred Hutchinson Cancer Research Center in Seattle.

Changing Risk-Benefit Ratio

The traditional informed consent model required researchers to explain possible trajectories at the outset; however, this was not appropriate for the study. "When it came time to select a subsequent treatment, it would be difficult for patients to remember a conversation that occurred weeks beforehand," says Krakow.

Conceivably, patients might refer to the original consent form as a reference, assuming they kept it — and understood it. "These documents are dense and long," notes Krakow. "And much of the information would not be relevant to the treatment choices at hand."

Even if patients fully understood all the complexities, an important piece of information still was missing.

"The risk-benefit ratio of the treatments proposed could not possibly be known at the outset since many clinical events would occur in the interim," says Krakow.

Some people initially appear to be good candidates for transplant. But complications of treatment, such as renal insufficiency, may develop — changing the risk-benefit analysis. It became apparent that a repeat consent conference was necessary before each sequential randomization.

This change raised broader questions of how best to inform cancer patients about the decisions they face in any randomized trial. As someone who regularly seeks patient consent for high-stakes experimental oncologic interventions, Krakow puts a lot of thought into how these trials are presented to patients: "Yet, I still don't think I communicate the nature of clinical trial participation well enough."

Krakow and a colleague sought answers in a recent analysis of 27 studies.[1] None of the studies specifically addressed problems posed by multiple sequential randomizations, but many of the issues were relevant. Some of the identified barriers to informed consent could be addressed fairly easily, including shortened consent forms or provision of a concise summary.

Deeply ingrained, flawed perceptions of medical research are considerably more challenging. "Beliefs such as the 'therapeutic myth' often lead patients to filter what they hear, and prove difficult to change," says Krakow.

The paper was rejected by two leading oncology journals. "The editors sent almost apologetic rejection letters," says Krakow. "They did not cite flaws in the paper, but noted that the findings would not surprise their readership."

To the researchers, this was an indication that problematic informed consent processes are commonplace. "This leads to the question of why we allow these inadequate methods of soliciting informed consent to persist ubiquitously," says Krakow.

Consent forms and processes

may provide some legal protections to clinicians. However, they are not serving the needs of patients, concludes Krakow.

The paper suggests that researchers consider newer, lesser-used methods, such as:

- animated videos;
- decision aids developed with the help of patients;
- the presence of trained patient advocates during patient/physician discussions on treatment options.

It is not uncommon for a provider to become aware of a significant change in the patient's medical or psychosocial condition from the time the consent form was signed. In this case, another conversation is needed about whether the patient wishes to remain in the study, says Krakow.

This is especially important if study-mandated treatment is ongoing, says Krakow. "The possible risks and benefits of receiving treatment might have changed substantially." ■

REFERENCE

1. Nathe JM, Krakow EF. The challenges of informed consent in high-stakes, randomized oncology trials: A systematic review. *MDM Policy Pract* 2019;1:2381468319840322.

FDA Streamlines Expanded Access to Oncology Drugs

'Project Facilitate' will use call center to speed process

The FDA Oncology Center of Excellence recently announced Project Facilitate, a pilot program seeking to streamline expanded access to investigational drugs in the era of Right to Try laws.

The project calls for a new call center, which will be a single point of contact for physicians seeking expanded access to investigational oncology drugs. FDA oncology staff will help physicians through the process of submitting the request for expanded access and follow-up as needed.

Jessica Boehmer, MBA, a regulatory scientist in the Office of Hematology and Oncology Products, outlined the benefits of the new approach at a recent FDA workshop. These include "IRB resource options," she said.

"Project Facilitate staff will be equipped to provide step-by-step support geared toward community providers who need access to an IRB where they practice," Boehmner said. "[FDA] will guide the caller to IRB resource options, pharma\biotech contact, and necessary information to complete the request as well as assistance in filling the form if needed."

As with other expanded access requests, physicians will not need preapproval from an IRB, but will need to notify the IRB within five days of treatment initiation, an FDA spokesperson says.

The first option for patients is to enroll in a clinical trial, but if that is not possible, oncology patients can seek investigational treatments through the project facilitate pathway. "[The FDA is] exploring ways to make it easier for patients, their families, and healthcare professionals to understand the process and how to access investigational therapies," Acting FDA Commissioner **Ned Sharpless**, MD, said in a statement.

The idea is to simplify the expanded access process, which Right to Try advocates have accused of being too cumbersome and bureaucratic, says **Carolyn Riley Chapman**, PhD, MS, a professor in the New York University Division of Medical Ethics.

"Oncologists can call and get guidance on how to submit the request. They can even call before they have gotten approval from a particular manufacturer about access," she says. "The FDA is opening its doors as a resource."

The pilot call center project will inform the FDA's efforts to streamline the expanded access process in general. For example, the longstanding approach for expanded access for cancer patients saw requests forwarded separately to various points within the FDA, including to the separate divisions for oncology and hematology.

"The pilot program includes a central office for oncology requests so that the FDA can follow up on individual requests and gather data, such as how many patients received the investigational medical products, and if not, why the requests were denied," the agency said in a statement. "The FDA can use this data to determine how the process is benefiting patients and healthcare professionals. In addition, the data could assist in encouraging sponsors to open clinical trials to study drugs for additional indications." ■

IRB ADVISOR

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CME/CE QUESTIONS

1. **Which of the following is a change in new guidelines published in April 2019 by the NIH?**
   a. The new guidelines eliminate the Genetic Modification Clinical Research Information System (GeMCRIS) database and the pre-review function of the replacement to the RAC.
   b. The new guidelines move 90% of genetic research into the expedited review category.
   c. The new guidelines start a new GeMCRIS database that gives regulators cross-referencing capability and information to quickly find adverse events related to gene transfer research.
   d. The new guidelines move human subjects protection responsibility in genetic research from IRBs to local IBCs.

2. **Which of the following is a risk IRBs could likely encounter when researchers use social media sites to engage with prospective subjects?**
   a. They might use these sites to collect follow-up health data on subjects.
   b. Investigators might post about their study's results pre-publication on Twitter.
   c. Researchers might use a social media page to generate interest among potential research subjects without disclosing their intentions.
   d. Researchers might share links to videos of subjects on social media pages.

3. **Harlan M. Krumholz, MD, SM, said not publishing human research data from clinical trials:**
   a. is acceptable if the results do not support the hypothesis.
   b. is criminal under the Helsinki Accords.
   c. does not affect recruitment because the trials are largely unknown.
   d. is academic misconduct.

4. **Which financial conflicts of interest influence whether studies report findings favorable to industry sponsors, according to a recent study?**
   a. Only undisclosed conflicts of interest
   b. All financial conflicts of interest
   c. Only relevant conflicts of interest
   d. Only conflicts of interest with $50,000 or more of payments