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INSIDE

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Common Rule Change Took Six Years to Complete — And Could Be Upended in 30 Seconds

Uncertainty is only known thing

By Melinda Young, Author

IRB and research experts find many improvements in the final rule on the Federal Policy for the Protection of Human Subjects. After six years of debate, criticism, and waiting, the 543-page rule looks a lot better than the original proposal in 2011, but the biggest question now is whether the work will be upended with the stroke of a pen.

"I'm not sure what to make of it at this moment," says **Alan Stockdale**, PhD, director of the human protections program and IRB chair at the Education Development Center in Waltham, MA.

"We've been waiting for the Common Rule for six years — a long time, and then it's announced on the last day of the Obama administration, and everyone is saying this could all be undone," Stockdale says. "It could be that in several months we'll be back to the same old-same old, and I have no sense of whether or not that will happen."

> "IT COULD BE THAT IN SEVERAL MONTHS WE'LL BE BACK TO THE SAME OLD-SAME OLD, AND I HAVE NO SENSE OF WHETHER OR NOT THAT WILL HAPPEN."

Stockdale spoke about the final rule in late January, just a few days before President Trump signed an executive order that required that "for every one new regulation issued, at least two prior regulations be identified for elimination."

The "one-in, two-out" order created the potential for recently published regulations, including the new Common Rule, to be quickly and easily overturned. Another way the final rule could be shelved is through the

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Congressional Review Act, in which lawmakers can repeal regulations approved in the last 60 days of a congressional session.

"No one thinks this Common Rule will be pulled out for individual treatment," says **William Smith**, JD, director of the IRB at Nova Southeastern University in Davie, FL.

Plus the Congressional Review Act's method of repealing regulations could be subject to a filibuster, Smith says.

As of *IRB Advisor*'s publishing deadline, the outcome remains unsure.

One argument that might save the new Common Rule from being swept away is that it was created to reduce human research protection regulatory burden, says **Erica Heath**, CIP, a retired IRB director in San Anselmo, CA.

Heath's advice to IRB offices is to make a list of potential changes under the final rule, but to not put too much time into creating new forms or standard operating procedures (SOPs) until everyone knows for certain if the Common Rule will stand.

Stockdale also recommends that IRB directors wait before implementing the changes and educating staff about the changes.

"I cannot imagine doing any of this until we're certain these regulations will stay in place," Stockdale says. "The uncertainty is a bit of a problem."

In the event the Common Rule survives, the following are key points IRBs and research institutions should know:

• The new rule reduces some administrative burden. "Overall, I think it does reduce the administrative burden for a lot of IRBs," Smith says. "It remains to be seen how it works because there is a requirement that federally funded studies use one IRB in the U.S. unless there's a compelling reason not to."

This could create complications as research organizations enter negotiations, he adds. *(See story on where final rule succeeds and falls short, page 27.)*

"It's a requirement, but it places more emphasis on the fact that it's not all clinical trials, just federally funded clinical trials," Smith explains. "Requiring this of industry-sponsored ones would cause massive headache and stress."

• Exemptions and expedited reviews are changed. "Operationally, almost all of the changes affect the low end of the review," Heath says. "That is the expedited review, the exempt review."

While the new Common Rule might not reduce the IRB's workload, it will change classification of some studies, Stockdale notes.

"Looking at it so far, my sense is that it is going to be a lot of process changes for the IRB," Stockdale says. "We can say, 'You're exempt,' and we advise people on consent, but when they're exempt, we don't have to approve their consent forms."

From the Education Development Center's perspective, some things treated as expedited involve secondary data, such as information from school records, and there is no consent involved, he notes.

"But we have to make sure that the data are appropriately protected," Stockdale says. "My understanding is that situation might be treated as exempt, but we would have to do a little extra IRB review to make sure there are appropriate data protections in there."

The final rule deems a minimal risk study to be eligible for expedited

review if it involves activities on the secretary's list. This is expected to move more studies to expedited review, relieving some burden on IRBs.

Studies undergoing expedited review no longer need continuing review, although reviewers can justify an exception.

"That's a big burden lifted on IRBs," Heath says. "I think you could get a lot of arguments about whether it does or does not reduce protection."

• **There is more attention on data protections and privacy.** "The changes reflect that data protection is a big issue, but we'd already gotten there as an institution years ago," Stockdale says. "It's like the regulations are catching up with reality: We were looking at data protection issues that weren't necessarily in the old regulations, but we thought were important."

Data privacy issues are among the biggest risks for social-behavioral research, Stockdale says.

"In doing educational research, protecting student privacy and compliance with the Family Educational Rights and Privacy Act [FERPA] is very important," he says. "One of the main risks for us in most of the research we do, particularly in the more sensitive research, interviews, or surveys with people related to violence or HIV, is data privacy."

• **The informed consent changes need more guidance.** "Consent needs a lot of guidance," Smith says. "I like that they emphasized the process of informed consent, but a lot of these phrases they use and the wording used to emphasize the process is really going to result in people wondering what it means."

• **Pregnant women no longer are considered vulnerable.** One change was to remove pregnant women from the list of vulnerable populations. "They've changed it to be vulnerable due to coercion or undue influence, such as children, prisoners, economically or educationally disadvantaged, and pregnant women are no longer vulnerable," Heath says. "Pregnant women are special in subparts — it's a change in viewpoint."

• **There is no self-determining exemptions.** "One thing I was concerned about with the NPRM was the proposal to have a tool for investigators to self-determine their study's exemption," Stockdale says. "I'm very glad they took that out, as it was a terrible idea."

There are more exemption categories, and these are complicated and will require time to review. But it's better that they eliminated the self-determination possibility because it would have been a compliance problem, he says. ■

Final Common Rule Is An Improvement, but Leaves Some Questions Unanswered

How to sort out central IRB roles?

There were many changes between the Notice of Proposed Rulemaking (NPRM) and the final rule, and even more changes since the Advanced Notice of Proposed Rulemaking (ANPRM), which is a good thing, IRB experts say.

"The ANPRM was shoddy, and not well worked out," says **Erica Heath**, CIP, a retired IRB director in San Anselmo, CA.

"The NPRM was better, but still pretty problematic; this version, however, is quite livable," Heath adds.

The final rule also has an estimated annual reporting burden in table 21. It's concise and readable, she says.

"This rule is literate, sensible, and meets their stated goals of reducing regulatory burden without really affecting protection, so it's come a long way," Heath says.

Another change is that the NPRM proposed to cover all biospecimens, regardless of their identifiability under the Common Rule, and the final rule does not require consent for secondary research with nonidentified biospecimens.

"They backed off from the worst in the NPRM," Heath says. "The original two documents would have precluded a lot of very important research."

For federally funded research using biospecimens, the rules are not as comprehensive as the original proposal, Smith says.

"The final rule is more concise about what you need to do, but leaves a lot to determine and more ways to segregate our federally funded studies from non-federally funded research," says **William Smith**, JD, director of the IRB at Nova Southeastern University in Davie, FL.

"They wanted people to make more use of flexibility," he adds.

Smith uses this example of the difference between the old Common Rule and the changes: "If you have a bucket of teeth, collected whenever someone had a tooth pulled, and you put these in a clinical depository," he says. "There are no identifiers attached to it."

If someone uses one of these teeth for research, then under the old regulations the teeth were not human subjects. But under the new Common Rule, if the tooth/biospecimen has an identifier and it's used for certain purposes that involve federal funding, then there are more conditions attached to its use in research, Smith explains.

"So now it makes sense for institutions to distinguish between studies that use federal funding and those that don't when they use data or specimens," he says.

Before, research organizations had the option of checking or unchecking the box in how they treated non-federally funded research.

"Now, they've taken away the box and everyone's box is unchecked," Smith says. "That's what the change in biospecimens will encourage institutions to do, creating a lot of requirements for biospecimens."

It will result in creating, maintaining, updating, and giving access to registries and specimen banks that institutions will have to distinguish between federally funded and non-federally funded biobanks and repositories, he adds.

One of the most controversial — judging by its more than 300 comments — NPRM proposals was the one mandating that all institutions in the United States engage in cooperative research and rely on a single IRB as their reviewing IRB for that study.[1]

According to commentary in the final rule, the comments on this change divided research institutions, which were generally against the change, and scientific organizations, which were in favor of the change. The final rule adopts the NPRM proposal with modifications, but not the modification many IRBs and research institutions had desired — that the single IRB review is encouraged rather than mandated.[1]

Instead, the final rule allows flexibility in implementing the change, giving institutions the option of conducting additional internal IRB reviews for their own purposes.

> "SMALL AND MEDIUM-SIZED IRBS WILL HAVE TROUBLE KEEPING UP THE PACE BECAUSE THEY DON'T HAVE THE STAFFING AND EXPERTISE ON HAND."

Those sorts of reviews would not have any regulatory status in terms of compliance with the Common Rule. The final rule also allows federal agency sponsors to select a central IRB, though lead institutions can propose the reviewing IRB and have their proposal approved by the sponsor.[1]

Further guidance will be needed, the final rule acknowledges.[1]

The net result will be confusion, especially since each central IRB arrangement will need to be ironed out legally, Smith predicts.

It can get complicated and frustrating because there is no template for such agreements, he adds.

"When you've got to worry about patient safety, who is going to do the local inspections and who has access to medical records?" Smith says. "Can you get the necessary documents, and will this streamline the review or will it be a case of every clinical trial having multiple negotiations over the contract, so it wouldn't save time — just waste time?"

Research institutions and their legal offices will be wary of being held accountable for another IRB's review, he adds.

"Lawyers are responsible for their clients' best interest, and if a clinical trial goes south for whatever reason, you don't want your client sued into bankruptcy because someone forgot to add a line in a consent form or to a clinical trial agreement," Smith says. "That's why they gave it three years to take effect."

While cutting back on multiple IRB reviews is positive, the lack of a template for these reliance agreements is a major issue, and it will affect some IRBs, he adds.

"Most of the IRBs like ours — medium-sized — won't close, but there will be a tendency to farm out reviews," Smith says.

Independent IRBs, which are accustomed to the agreements, will benefit because they're very good at handling these reviews quickly, he says.

"Small and medium-sized IRBs will have trouble keeping up the pace because they don't have the staffing and expertise on hand," he says. ■

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Strategies to Better Manage Noncompliance

Systemize noncompliance reporting

The IRB at the Biomedical Research Alliance of New York (BRANY) in Lake Success, NY, noticed a problematic trend of researchers amending their studies in the continuing review reports.

The IRB has a reportable event form, but these changes were not always being submitted that way, says **Raffaella Hart**, MS, CIP, vice president for IRB and IBC services at BRANY.

Sometimes a week or more would pass before the IRB knew that there was an issue that needed action, she adds.

"We had a channel for reporting noncompliance, but people didn't use that channel because they didn't think it was noncompliance," Hart says. "They'd say, 'We have a deviation,' but not use the right channel."

For example, a study team would use the wrong version of an informed consent form and think this was only a minor deviation. When IRB staff investigated it, they'd discover the new information was very important for people to receive in a timely fashion, she explains.

"We sent our auditors — the quality assurance team — to evaluate and help investigators learn how the consenting process should be," Hart says.

Once the IRB addressed noncompliance in a systematic way, the IRB's overall data processing time improved. For instance, data show an average processing time in 2013 of 62 days, versus 22 days in 2014, after the change.[1]

The following is how the IRB achieved its positive results:

• **Educate the IRB team.** They gave team members examples of how researchers were not using the correct forms to disclose changes, which resulted in noncompliance, Hart says.

"We educated the team to recognize reports that arrived in a way that we didn't expect, but which might show noncompliance that needs to be acted on," she explains. "For example, when a minor deviation report comes in and it doesn't look so minor based on the description, then consult with a staff person."

One example was of a case where a researcher sent in a minor development report, saying the study files were lost. "Our team said that didn't seem so minor," Hart says.

• **Educate researchers.** "We educate researchers about the best way to accomplish prompt reporting," Hart says. "Sometimes, they didn't realize that a particular incident needs to come to us on a reportable event form."

The IRB's website provides detailed information and education with links to forms and instructions. For example, the Minor Protocol Deviation Log can be downloaded to list deviations and this information:

- date of deviation,
- patient ID,
- associated visit,
- deviation type,
- description of deviation,
- action taken, and
- if applicable, sponsor notification date.

The form states that it is used to "record minor protocol deviations, which are defined as any temporary alternative/modification to the IRB-approved protocol that do not affect subject safety, rights, welfare, or data integrity. This may include administrative and minor departures from the IRB-approved protocol that do not affect the scientific soundness of the research plan."

The IRB created guidance on reportable events, explaining what needs to be reported, how, and when. The five-page guidance outlines examples of unanticipated problems involving risks to participants and others.

For instance, it says that examples may include onsite and offsite adverse event reports, injuries, side effects, breaches of confidentiality, deaths, or other problems that occur any time during or after the research study, provided they meet the following three criteria:

- involve harm to one or more subjects or others, or placed one or more subjects or others at increased risk of harm,
- unexpected, and
- related to the research procedures.

Other unanticipated problems could involve a change to the protocol taken without prior IRB review or incarceration of a participant or a protocol violation that places a participant at increased risk, the guidance states.

"Our website publishes a little graphic that has the types of submissions that need prompt reporting, timelines, and the form to use — to make it easier for people," Hart says. "We updated the instructions on all of our forms to

say that if you are trying to submit a deviation report, then you are on the wrong form."

The education receives positive feedback. "The feedback we got was that sometimes people didn't realize certain types of events fit into the noncompliance category, and they didn't realize they were doing it wrong," Hart says.

• **Make workflow improvements.** "We built in workflow so if certain things are flagged, certain people will get alerts about them," Hart says.

For instance, there are electronic alerts that are sent to a designated person in situations such as when someone indicates there is an unanticipated problem and submits a form, she explains.

"We find that is helpful because there is a lot of stuff going at one time in a study," Hart says.

• **Use dedicated IRB staff.** The IRB has someone who is trained to handle noncompliance and unanticipated problems, but also has other duties.

"It works out because there's not a steady flow of these things," Hart says. "They ebb and flow, and sometimes people are doing a good job with no problems and then sometimes there is a rash of problems."

The IRB also runs a report of noncompliance and unanticipated problem events on a bi-weekly basis.

The process appears to be working well, and the IRB staff and researchers are comfortable with it, Hart says.

"Our dedicated reviewer made suggestions about modifying the electronic reporting form so questions would elicit information that was more helpful to them, and we're in the process of implementing that," she says. "We meet monthly to check and make sure the process is going smoothly and to see whether staff have any suggestions for improving it." ■

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Inexact Science: The Complicated Quest To Replicate Research

A host of variables can confound the process

Initial findings of a new study[1] on cancer research appear to bolster the emerging consensus that clinical trials have a "reproducibility" problem — meaning attempts to replicate trials cannot always produce the same results. But a deeper look into the actual mechanics necessary to reproduce a trial reveals a process that is beset by variables that make clear conclusions difficult, one of the authors argues.

"It is hard to replicate something because there are so many factors that could influence it," says **Timothy Errington**, PhD, manager of metascience at the Center for Open Science at the University of Virginia in Charlottesville.

Thus, the Reproducibility Project at UVA has undertaken an elaborate attempt to replicate prior research, with the recently published results focusing on cancer research following a similar effort on psychology trials. Efforts were particularly made to ensure that replication failures were not caused by errors in the reproduction experiments. Errington and co-author concluded, "The results of the first set of replication studies are mixed, and while it is too early to draw any conclusions, it is clear that assessing reproducibility in cancer biology is going to be as complex as it was in a similar project in psychology."

An emerging body of research reveals that past studies — some of which may form the basis of current policies and recommendations — cannot be replicated by investigators today. This lack of "reproducible" research may undermine current studies based on prior findings, particularly as investigators look at the risk-benefit ratio for people participating in a clinical trial. Some studies of the problem estimate that as much as 50% or more of published results in biomedical research cannot be validated.[2]

In an attempt to address these concerns and shed some much-needed light on the subject, the UVA researchers attempted replications with high statistical power and sought to authenticate the original key biological materials in studies designed to avoid bias. In addition,

"the authors of the original papers were contacted in advance for details of the research methodology that may not have appeared in their paper, and were asked to share any original reagents, protocols, and data in order to maximize the quality and fidelity of the replication designs," the researchers reported.

In the end, they were left with "mixed" results that were not reduced to a percentage of reproducibility at this phase, prompting instead such caveats "that there is no such thing as exact replication because there are always differences between the original study and the replication. These differences could be obvious — like the date, the location of the experiment, or the experimenters — or they could be more subtle, like small differences in reagents or the execution of experimental protocols."

In addition, a failure to replicate does not necessarily mean the original research was incorrect, the authors concluded.

"It is possible, for example, that differences in the methodologies that were thought to be irrelevant are actually important," the authors noted. "Indeed, a failed replication can lead to a better understanding of a phenomenon if it results in the generation of new hypotheses to explain how the original and replication methodologies produced different results and, critically, leads to follow-up experiments to test these hypotheses."

Scientific coverage of the findings was less equivocal, with one journal concluding, "Of the five studies the [cancer research replication] project has tackled so far, some involving experimental treatments already in clinical trials, only two could be repeated, one could not, and technical problems stymied the remaining two replication efforts."[3]

IRB Advisor asked Errington to comment on this and other aspects of this complex project.

IRB Advisor: Is the assessment correct that only two of five cancer research results from prior trials could be replicated?

Errington: At this stage — and even at the end — we try not to label. The truth is we don't know what a lot of this means. That is [the journal's] opinion, and that is important, but we are actually interested in exploring this further. You talk to some people and they would say, "None were replicated." Others would say, "Things look just fine." Two of them came up with technical issues — what that really means is that in the replication, the experimental systems behaved differently. So, whether that is technical or that is actually what occurred originally but was not reported is kind of hard to separate. Those [comments] are really broad strokes, and the truth is, there is a lot more nuance to this. That's what we are trying to get into — and to actually discuss that more in detail.

WE ARE MAKING GREAT LEAPS IN KNOWLEDGE, BUT WE ARE PROBABLY NOT BEING AS EFFICIENT AS WE CAN IN THAT ENTIRE PROCESS.

IRB Advisor: This initially has been presented as a kind of a general widespread problem, but you cite a host of variables that could undermine replication efforts, adding a considerable level of complexity to the whole question.

Errington: That's all the more reason to try to improve this process. We are making great leaps in knowledge, but we are probably not being as efficient as we can in that entire process. We should be able to minimize the variance that occurs just from our own communications as scientists, or our own incentives to only publish part of the results versus everything. We can definitely change the behavior to expose more of it.

The other thing is because it is hard to replicate — which really means because it is hard to do research — we often need to be very cautious how much weight we put on any one study. Just because someone has published a study and nobody has replicated it, that doesn't dismiss the original, but it doesn't mean we should put too much [weight] on the original. It's one piece of evidence. It's important to recheck that piece of evidence to ensure we have reliable [research] and not just assume that. We need to put that in context. We do want to be able to try to trust our research as much as possible. If we can't, OK — let's figure out how we can improve it so that we can build on each other's work more efficiently.

IRB Advisor: Is one of the goals of your work to develop a process or methodology to look at this problem?

Errington: This project is one way of doing that. It is difficult because we don't incentivize replications and the showing all of [research] processes. We're doing these projects as a means to get a rate [of reproducibility]. Nobody reports these [and there's not an accepted method] of figuring it out. So this project is an initial attempt to say, "Well what is that method?" It would also be good to have complementary mechanisms that ask, "How can we better track all of the studies that are going on?"

Because right now, that is locked away — what we see is what they publish. What they publish are positive results.

IRB Advisor: How does this project compare to your previous reproducibility study[4] of psychological research?

Errington: That abstract describes five different ways to examine reproducibility, but we still really don't know what that means. Everybody wants to put [a number on it], but we don't understand it. Unfortunately, everybody just latched onto the number 39% [of studies that were reproducible] when they reported on it. But the truth is that both of these projects have already exposed common themes, [including] not being able to have access to all the data, the materials, and the methods. That was a big challenge even getting our [cancer research] project launched, and it was a similar problem in psychology. These [general problems] are not unique to the [scientific] disciplines — maybe the aspects are different — but there are shared commonalities across all of science that can basically hinder reproducibility, and there are ways to improve these.

IRB Advisor: What are some of the obstacles that have to be overcome?

Errington: Right now there is a lot of emphasis on getting positive results, doing it very quickly, and getting novel findings. What that generally leads to — and with the psychology study we had the same thing — is that you have these small sample sizes. [Our replication experiments] — every single one, I think — had a higher sample size than the original because we are powering up our experiments to find useful effects. Say, instead of using five mice per condition, we are using 15-plus mice per condition. You don't want to use too many because that is wasteful in terms of resources and lives, but if you use too few and too many people do that, you can get misled really quickly." ■

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Clinical Trials: More is Not Necessarily Better

Amid a rising tide of research, IRBs should look for 'social value'

While one may reasonably assume that more clinical research could increase the likelihood of medical breakthroughs, a contrarian's view is that the effect could be quite the opposite — and it falls to IRBs to intervene and reduce the risks of the current glut of trials.

"It probably seems intuitive to most people that if research is good, then more research is better," says **Kirstin Borgerson**, PhD, associate professor of philosophy and a bioethics researcher at Dalhousie University in Halifax, Nova Scotia. "But we know that many studies conducted today are of low quality. For instance, they are too small to produce statistically significant results, or have unjustified exclusion criteria. When these low-quality trials are published alongside high-quality trials, and when both are published at astonishingly high rates — as they are today — this leads to what I call the 'sorting problem.' Basically, anyone wanting to make use of the research evidence has to first sort through hundreds, and even thousands, of bad studies to find the good ones. Alongside skill and effort, this takes time, and that means that research is slow to filter into practice."

In a recent paper[1] on this situation, Borgerson cited studies that document the problem, with one concluding that "every day there are now 11 systematic reviews and 75 trials, [published] and there are no signs of this slowing down — but there are still only 24 hours in a day."[2] Other studies estimate that medical research output doubles every seven years, and to date, some 1 million clinical trials are in print.[3,4]

"Even if it were true that all research was good — that is, high quality — at some point the publication output would exceed the time available to clinicians for reading and critically assessing those studies," she

says. "And if clinicians then turn to experts to do this critical work for them, they are faced with challenges in determining which experts to trust since so many have their own agendas. They also have to allow those experts to apply some rules of evidence — all of which have shortcomings and limitations that aren't always acknowledged. So even in this ideal scenario, things aren't straightforward."

Borgerson argues in the paper that the "overproduction of low-quality clinical research is very likely to be harmful to patients. On ethical grounds, there are persuasive reasons to endorse the position that we should conduct fewer clinical trials. Researchers and research ethics committees should work together to ensure that trials truly benefit society, as they are meant to do."

In that regard, IRBs should look at research that has "social value" and pragmatic implications for patients, she notes. Borgerson cites tools like PRECIS (Pragmatic Explanatory Continuum Indicator Summary) and PRECIS-2.[5] The latter provides nine areas to assess trial design, including eligibility criteria, recruitment, setting, and primary outcome.

"In general, the more these design elements match usual care, the more pragmatic the trial," Borgerson notes in the paper. "… There is growing support for this position, for instance, in trends toward comparative effectiveness and translational research, research-practice integration, and quality improvement studies."

That said, there may be disincentives in place that may give pause to IRBs or researchers wanting to adopt such strategies, Borgerson concedes.

"There may be some sense that requiring that trials are assessed for social value, using a tool like PRECIS, is overreaching on the part of IRBs," she says. "Researchers don't always respond well to ethics committees that question their methods — there seems to be this idea that science and ethics are entirely distinct from each other. I think this is just false, but it is nevertheless a view that will impede efforts to move in a pragmatic direction."

In addition to the challenges of fighting this battle, IRB members may feel unqualified to assess the design of a study, uneasy with the idea of predicting future social value, or be already so overworked that the idea of adding further work is disheartening, she says.

> "ON ETHICAL GROUNDS, THERE ARE PERSUASIVE REASONS TO ENDORSE THE POSITION THAT WE SHOULD CONDUCT FEWER CLINICAL TRIALS."

"These are all real — and serious — concerns, many having to do with the support and training available to IRB members," Borgerson says. "What I try to emphasize in the paper is the fact that the obligation to assess the social benefits and social harms of all research trials is already a responsibility of IRBs. I am just identifying a particular harm of permitting poor-quality studies to proceed — they contribute to the sorting problem. So, IRBs can't really ignore this responsibility."

Small sample sizes may certainly limit extrapolation to other patient populations, but there are several factors to consider before drawing an arbitrary minimum line for trials to move forward.

"There will be exceptions for Phase I trials and research on orphan diseases — and, of course, different methods and questions will require different cut-offs," she says. "But otherwise, yes, I think that trials that are too small, or which are likely to fall short of recruiting enough participants, shouldn't be conducted."

Another issue that is being reported with concern is that a surprising number of clinical trial findings cannot be reproduced. We asked Borgerson if this should be factored into the equation.

"I've been following this debate over reproducibility and it seems that failure to reproduce results is sometimes the result of poor quality in the initial study," she says. "That suggests to me that we can make some progress on the reproducibility problem by ensuring that all studies approved by IRBs are genuinely high-quality studies, which is exactly what I argue for in the paper." ■

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Military IRBs May Err on the Side of Bureaucracy

Does intuitional risk trump research subject protections?

IRB delays in federally funded research in the U.S. military "often appear in the service of managing institutional risk, rather than protecting research participants," researchers report.[1] Military IRBs may thus "err on the side of bureaucracy," but the delays can place unnecessary burdens and risks on human research subjects.

On the other extreme, "military members are exposed to untested or under-tested interventions, implemented by well-intentioned leaders who bypass the research process altogether," study authors warn.

Overall, "the IRB review process within the military is viewed as more opaque, unpredictable, slow, and adversarial than what [we] have experienced in other U.S. government, public, and private settings, as well as in anecdotes presented in the literature," the authors concluded. We asked the lead author to comment on the findings, and **Michael C. Freed**, PhD, EMT-B, of the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, MD, and licensed psychologist and owner of Capital Behavioral Health & Wellness, LLC, provided the following answers.

IRB Advisor: The delays described seem to be often bureaucratic, but could an argument be reasonably made that perhaps human research and ethical oversight involving military subjects should proceed at a slower pace than research in general? For example, trials may involve something like anthrax vaccine for this special population, or any research-supported intervention could be "mandated," given the command structure of the military.

Freed: In the paper, we argued for an efficient administrative process to ensure research protocols receive timely reviews. Delays have adverse effects on studies and create unnecessary burden on study participants that are usually overlooked. Rigor in the review is important, as is timely return of review results. We did not argue for an expedient IRB review at the expense of thoughtfulness and rigor. While pace of review might be equated with rigor, one needs to be mindful to not conflate the two.

In our "Case Example 1," [dealing with post-traumatic stress disorder in veterans] we took no issue with the review of the IRB itself. Rather, we experienced challenges with the administrative processes at the front and back end of the review process. To your point, yes, high-risk studies should receive increased scrutiny. IRBs do this already (e.g., expedited and exempt reviews). But again, increased rigor does not necessarily necessitate a slower pace of review.

IRB Advisor: That said, you clearly state that, "we accept the necessity of regulatory review and see its value in protecting human subjects from harm and ensuring quality of research." Can you discuss a few of the practical solutions proposed to streamline the process without increasing risk to research subjects?

Freed: Sure. We make the case that more review is not necessarily better or safer review. We make a few pragmatic suggestions:

- Standardization of IRB processes and forms across the Department of Defense.
- Priorities for federally funded studies, rather than priority of protocol receipt.
- Transparency of processes and the collection of metrics to help with accountability, identify bottlenecks, and create benchmarks which can be measured and improved.
- Examination of the order and necessity of a science review, in places where this happens.

Of note, we were equivocal on a centralized IRB as a suggestion, as a centralized system would not necessarily guarantee a more efficient review, as bottlenecks could still occur.

IRB Advisor: In what seems to be analogous to the old "justice delayed is justice denied" adage, you and colleagues raise the point that a stalled review process may give rise to ethical questions about the research and human subjects. Can you please elaborate on this concern and the ways that IRBs should figure this into their overarching goal of ensuring safe, ethical research?

Freed: The adage is a nice analogy. If studies cannot be completed properly because of IRB-related administrative delays, then the burden to participants is, by definition, unnecessary. What we are talking about here is about protecting research participants from undue burden — harm. In our "Case Example #2" [in which a military commander decided to proceed with use of fatigue monitoring devices for helicopter pilots after prolonged IRB delay], military leaders who wanted to implement and use the device in the field were not required

to follow IRB protocol. Presumably, there were other administrative controls in place, but I cannot speak to those. We attempted to highlight an issue, which speaks to scope of IRB influence and the challenges with trying to align a time-sensitive opportunity for research with a regulatory system charged with ensuring human subjects protection. To the extent the IRB delay here was administrative, then our suggestions above may have helped researchers secure a definitive answer sooner.

Editor's note: Dr. Freed wishes to state the views expressed are those of the author(s) and not necessarily those of USUHS or any other organization, public or private. ■

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Teleconsent Boosts Recruitment of Rural Research Participants

One barrier to recruitment of qualified research participants for clinical trials is the cumbersome, time-consuming consent process. Another is the lack of access to participants in remote locations.

Teleconsent, a novel solution developed by researchers at the Medical University of South Carolina (MUSC) in Charleston, addresses both of these difficulties.[1]

"We developed teleconsent to address a major challenge, which was to recruit and consent research participants in a largely rural state," says **Brandon M. Welch**, MS, PhD, assistant professor at MUSC's Biomedical Informatics Center.

The researchers began exploring alternative ways to obtain consent that didn't require travel, either for the researcher or participant. They came up against similar difficulties with mail, fax, and electronic consents: There is no easy way to verify that the participant actually understood what he or she signed. It's also difficult to verify the prospective candidate is the one completing the form.

"Having the ability to actually see the participant while they are completing the document is the key innovation over other solutions," says Welch.

Not everyone has a computer with an internet connection, which is needed for a teleconsent call. This raises ethical concerns involving access. "We are currently addressing this issue by making teleconsent available on smartphones," says Welch.

The group is working on a way for researchers to design and build their own electronic consent documents. "We're also interested in integrating other features that support clinical research, such as survey forms, and devices for data collection and transfer," says Welch.

Researchers still obtain consent in person in the vast majority of cases. They use teleconsent only when the participants can't be accessed in person.

"Teleconsent is intended to complement, not replace, the traditional consent process," notes Welch. Teleconsent makes it easier for researchers to recruit rural participants, who are typically underutilized in research.[2]

"I've heard researchers make the argument to our IRB that they are ethically bound to use teleconsent to be as inclusive as possible of those who are typically not represented in research studies," notes Welch. ■

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COMING IN FUTURE MONTHS

- Create thorough clinical research training and mentoring program
- Which IRB regulations could be shelved in 2017?
- Innovations in informed consent
- Best practices in adverse event monitoring

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.
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CME/CE QUESTIONS

1. **Which of the following was the chief goal of the revised Common Rule?**

   a. To add deeper protections to the IRB review process through additional regulations.
   b. To reduce human research protection regulatory burden and streamline the IRB review process.
   c. To force independent IRB use for industry-sponsored clinical trials.
   d. All of the above

2. **What is the purpose of creating a Minor Protocol Deviation Log?**

   a. To create a database of researcher "bad actors."
   b. To record serious unanticipated problems.
   c. To record minor protocol deviations, defined as any temporary alternate/modification to the IRB-approved protocol that do not affect subject safety, rights, welfare, or data integrity.
   d. None of the above

3. **Timothy Errington, PhD, said efforts to replicate research in psychology and cancer studies had what common theme?**

   a. Lack of access to all the data, materials, and methods.
   b. Small studies had surprising statistical power.
   c. Many studies thought to support the same clinical practice actually reached very different conclusions.
   d. All of the above

4. **Kirstin Borgerson, PhD, said IRBs could reduce rapidly expanding research by:**

   a. prioritizing studies that have a small sample size.
   b. declaring moratoriums on research in certain areas.
   c. applying principles of social value and pragmatism to IRB review.
   d. addressing the "sorting problem" through electronic records.

CME/CE OBJECTIVES

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

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