IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

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EU Will Require More Clinical Trial Transparency — Will U.S. Be Next?

Sponsors have to give simple-language study results

By Melinda Young, Editor

The European Union (EU) soon will require investigators to give people the kind of transparent, easy-to-access clinical trials information they've been conditioned to expect in the age of Google.

In 2017, researchers and clinical trial sponsors with sites in the EU will need to create lay summaries of study results and make these available to research participants. The EU's move to increase transparency is following a trend that the human research protection industry also is noticing in North America.

> THE EU'S MOVE TO INCREASE TRANSPARENCY IS FOLLOWING A TREND THAT THE HUMAN RESEARCH PROTECTION INDUSTRY ALSO IS NOTICING IN NORTH AMERICA.

Returning general clinical trial results, which is different from giving individuals their personal clinical trial information, is a growing trend that's reaching a tipping point, says **Ken Getz**, MBA, associate professor and director of the Center for the Study of Drug Development at Tufts University in Boston. Getz also is the founder and board chair of the nonprofit Center for Information and Study on Clinical Research Participation (CISCRP).

Companies increasingly are considering piloting a trial results disclosure initiative, partly in response to the patient centricity movement, Getz says. *(For more information on how and why to return results, see related story on page 112.)*

"There's this growing recognition that returning trial results is the ultimate act of appreciation, and it's

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also sort of integral to ensuring that our study volunteers are engaged as partners in this research process," Getz adds.

The U.S. Department of Health & Human Services (HHS) Secretary's Advisory Council on Human Research Protections (SACHRP) addressed the issue of sharing general study data and results with subjects first in 2013 and, also, in later commentary.[1]

SACHRP said federal agencies should take steps to promote the return of general results to subjects, starting with the FDA, which needs to provide clear guidance on how clinical investigators and sponsors can avoid promotion of medical products when providing general results to subjects. Also, there needs to be agency guidance on whether an IRB needs to review the communications of research results to subjects, according to SACHRP.[1]

"The European Union is pioneering the evolution of trial results summaries into plain language, and we see that as an incredible new development," Getz says.

The European Parliament in May 2014 published the European Clinical Trial Regulation (EU No. 536/2014) that explains new requirements for authorizing, conducting, reporting, and providing transparency in all clinical trials that have at least one EU member site.[2]

Sponsors and investigators have to disclose results in a way that the average person can understand, including comments on the outcome of the trial.[2] *(For more details on the EU requirement, see related story on page 111.)*

In 2008, the United States required a return of generalized clinical trial results eight years after the NIH launched the database ClinicalTrials.gov. U.S. sponsors were required to post their studies' summary results on the website. But sponsors were not mandated to write the results in language that non-scientists/doctors would understand, as the EU has stipulated.

"The tipping point is that the European Union has passed regulations requiring the return of a layperson-understandable trial result," says **James Riddle**, MCSE, CIP, CPIA, vice president of client services at Kinetiq, a division of Quorum Review IRB in Seattle.

"It's time to ask, 'Should the United States follow the EU and finally get understandable results back to subjects, whether the results are good or bad?'" Riddle says.

The clinical trial enterprise has not done a good job of communicating the importance of participants' contribution, he says.

"There's growing evidence that the clinical trial community should and needs to develop a way to get information back to participants to facilitate clinical research and gain their trust," Riddle says.

Returning aggregate results to people who volunteer for research is something that is becoming increasingly important, says **Mitchell Parrish**, JD, RAC, CIP, vice president of legal affairs for Kinetiq.

"Nationally, it's in line with dissemination of information as we see through the internet and social media," Parrish says. "People have more access to information, and in our field there's a natural push because researchers can benefit by keeping participants involved and engaged."

But it's also complicated. Parrish notes that returning generalizable results raises the following questions:

• What information is meaningful enough to disseminate?

• What are the actual data that should be presented?

• What is the best method for providing data in a way that is understandable to a layperson?

• Should data be presented in graphic form, or in an interactive PowerPoint?

"We'll always need a written explanation, but we need to keep it short, concise, understandable, and couple it with graphics," Parrish says. "Graphics help people connect and understand results."

IRBs are well-positioned to help answer these questions because of their experience with shaping consent forms and making those easier to understand from study volunteers' perspective, Parrish adds. "Now, it's a natural progression for IRBs to collaborate with sponsors and researchers to come up with the best way to send information back to participants in a way that is understandable."

Also, there eventually might be a debate on whether these layperson summaries will require IRB review, he says.

"It might be up to the sponsor or researcher to make a judgment call and ask if they need feedback from someone who has experience in this field," Parrish says.

The EU regulation addresses informed consent, clarifying the use of data obtained based on informed consent.[3]

CISCRP began a program for communicating trial results six years ago, partly in response to demand from study volunteers of whom 97% want to receive the results of their clinical trial, but fewer than 10% ever do see the results, Getz says.[4]

"The FDA, for a long time, has been encouraging the transparency and disclosure of trial results information, and they've been supportive of nontechnical, lay language," Getz says. "The European Union jumps into the fray, and they're in synch with the FDA's perspective, but they're the first to come out and say that within one year after a trial has ended, they want to see sponsors making a summary and giving results that are understandable to the lay public."

CISCRP has helped lay the framework for providing generalized clinical trial results to study volunteers. "I'm very supportive of the work CISCRP and others have done in laying the framework for how we should be doing this," Riddle says.

"This seems to be the right moment to have industry sponsors

European Union's Requirements for Returning Trial Results

Ten elements needed

The European Union's European Clinical Trial Regulation requires clinical trial sponsors to create layperson-friendly content for the summary of results. Here are the required 10 elements:

1. Clinical trial title, protocol number, EU trial number, and other identifiers.
2. Sponsor's name and contact information.
3. General clinical trial information, including where and when the trial was held, its main objectives, and why it was conducted.
4. Information on the subject population, including the number of people included in the EU member state concerned, in the EU, and in other countries, as well as the age and gender breakdown and inclusion/exclusion criteria.
5. Investigational medicinal products used.
6. Description of adverse reactions and their frequency.
7. Clinical trial's overall results.
8. Comments on the clinical trial's outcome.
9. Indication if follow-up clinical trials are foreseen.
10. Where to find additional information.[1]

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really embrace this idea and to have the research ethics community and IRB community facilitate the return of results in some fashion," he adds.

For example, as NIH pushes for more central IRB reviews, the IRB that reviews the protocol could be in the best position to review the layperson summary created to share the study's results, Riddle suggests. "They would be in a position to help facilitate the distribution of the layperson summary and to get results back to a majority of sites." ■

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The How and Why of Returning Study Results

Short answer: It's a 'Thank you'

Returning a layperson summary of study results to research volunteers is the right thing to do that also could benefit the research community, several human research protection experts say.

"As a society, you start to see the desire in those who want to give back or have altruistic activities to know what their contribution means," says **James Riddle**, MCSE, CIP, CPIA, vice president of client services at Kinetiq, a division of Quorum Review IRB in Seattle.

It's a trend that's similar to how people increasingly want to know how their financial gifts to nonprofits are being used, he notes.

"People ask, 'What does this gift of my time, money, resources, mean, and does it do anything?'" Riddle says. "And it spills over to their participation in clinical trials research: They want to know what it meant and whether it made a difference, and if we don't provide any feedback, then we lose the opportunity to engage them in the next study."

The human research protection community has a general consensus of increasing awareness and openness in research, and this contributes to a growing trend toward returning results, says **Mitchell Parrish**, JD, RAC, CIP, vice president of legal affairs for Kinetiq.

"We think it's a good thing to return results to individuals in language that's understandable to them," Parrish says. "This improves patient engagement and shows respect for their participation."

Engaging research volunteers through returning generalized results also might help improve the industry's study recruitment rates.

As clinical trials become increasingly complex and difficult to execute, success rates are at a nadir and recruitment rates are continuing to drop, says **Ken Getz**, MBA, associate professor and director of the Center for the Study of Drug Development at Tufts University in Boston. Getz also is the founder and board chair of the nonprofit Center for Information and Study on Clinical Research Participation (CISCRP).

"We're targeting smaller and smaller markets with very targeted subpopulations, which makes it harder to recruit," Getz explains. "We need a new model, a new approach, and there's a moral imperative that patients have the right and ability to be engaged in this process."

CISCRP has a communicating trial results program, which has more than 30 sponsor companies. It helps organizations disclose results by providing post-trial communication, convening independent editorial panels to prepare lay language summaries, producing final summaries, and distributing printed material to site staff for dissemination.

"We have some companies now that are providing trial results to all their study volunteers through the CISCRP program," Getz says. "Our goal is to create a standard practice and help, if possible, every single company do this."

CISCRP's standard operating procedures (SOPs) can be integrated into a company's own trial results development activity.

"We engage the investigative sites and make sure the principal investigator and study coordinator

are aware that the results have been made available," Getz says. "We always do this with the research sponsor's support and technical summary, and the lay editorial board develops the plain language summary, which is reviewed by scientific experts for accuracy."

The bottom line is that giving research volunteers the results is a way to thank them for their service. "We view this as the ultimate act of appreciation, and a critical part of the whole patient and study engagement process," Getz says. ■

Olympic Athletes, Staff Enrolled in Zika Virus Study

Researchers study presence in body fluids, effect on pregnancies

In an ongoing study of 1,000 U.S. athletes, coaches, and staff that recently traveled to Brazil for the Olympic Games, researchers are doing antibody testing to see if any acquired Zika virus. Those that show evidence of infection have agreed to long-term follow-up to determine if Zika persists in body fluids.

According to the study protocol by researchers at the University of Utah in Salt Lake City, a web-based reproductive health survey will be conducted eight weeks after travel to Brazil and follow-up will continue for at least one year to assess for pregnancy in female travelers and in the female partners of male subjects. Those who have identified pregnancies will be surveyed quarterly through pregnancy completion or termination to ascertain fetal/infant outcomes.

PCR testing will be done for blood, saliva, urine, semen, vaginal secretions, and breast milk. Comparative research will be done for those reporting symptomatic Zika infection versus asymptomatic, the latter of which occurs in about 80% of people who acquire the emerging virus. In addition, the researchers will compare reproductive outcomes in those with symptomatic versus asymptomatic Zika infection, including the ability to achieve and sustain pregnancy to term.

Carrie L. Byington, MD, professor of pediatrics and co-director of the university's Center for Clinical and Translational Science, is the lead researcher for the study. She fielded the following questions for *IRB Advisor*:

IRB Advisor: What assurances did you provide your IRB regarding the confidentiality of the data gathered, and what steps were taken to ensure there was no suggestion of coercion to participate?

Byington: The study is de-identified, so participants will not be identifiable. All data are stored in a HIPAA- and FISMA-compliant database. All data will be reported in aggregate and no specific participant will be identified. All samples are labeled with a code and will thus be anonymous in the testing laboratories. No data will be entered into the electronic health record of the University of Utah. The study is voluntary and there is no penalty for those who choose not to participate. Potential participants received information about the study and have the opportunity to speak with study personnel to have all questions answered. There is no compensation. The U.S. Olympic Committee did not mandate participation.

IRB Advisor: Can you tell us a little more about the testing and follow-up aspects of this study?

Byington: We are testing antibodies in all 1,000 participants, so we will be able to identify Zika virus infection in both symptomatic and asymptomatic individuals. For those who test positive for Zika virus, we will test body fluids monthly until clear. We anticipate testing most individuals for up to six months, but are able to extend this testing window to 24 months if needed. We are interested in following any pregnancies that might occur in Zika-exposed participants, as we believe the extent of Zika virus infection in infants has not been fully described.

IRB Advisor: Since elite athletes are in peak physical condition, is it possible their physiology could introduce a variable that makes the results harder to extrapolate to general populations?

Byington: It is possible that elite athletes might have different physiologies; however, we are enrolling athletes, coaches, and other staff. Our athletes include Olympians and Paralympians. There is a wide range of ages and physical conditions represented that will allow the findings to be more generalizable. We believe all participants are at similar risk for Zika exposure and most will be naive to Zika prior to travel. ■

IRB Coordinators Can Get a Lot Done in a 30-minute Sit-down

Meet, show, educate, approve

The IRB of Oregon State University has found that short, in-person meetings with researchers can result in greater communication, collaboration, and efficiency.

"We've received unbelievably positive feedback from researchers about how much easier it is, and they've submitted more applications, as a result," says **Jillian Coleman**, CIP, human research protection program (HRPP) coordinator at Oregon State University.

Several efficiency improvements have occurred since the change. One is that researchers submit applications that are more thorough and do not need changes. Another is that the quality of the applications has improved so much that scheduled appointments can be cancelled, as no changes are necessary, Coleman says.

The meetings, which are both sit-downs and remote via videoconferencing, are scheduled for a variety of reasons, including the following:

- pre-submission advising,
- determining whether IRB oversight is necessary,
- review of exempt applications,
- assistance with responses to stipulation notices for expedited or full board reviews, and
- review of minor revisions to an expedited or full board study.

"We encourage researchers to schedule 30-minute appointments, and we ask them to submit their documents the business day before the appointment," Coleman says.

All appointments are held on Wednesdays, between 1 p.m. and 4 p.m., or Thursdays, between 1 p.m. and 5 p.m. Two or three HRPP coordinators will take the meetings each of those days. "Typically, people can get on the schedule the week they call, but sometimes we're booked," Coleman says.

"HRPP administrator Lisa Leventhal came up with the whole process and spends a lot of time thinking about how to make the process more efficient and meaningful for faculty," Coleman says. "She sat down with all of us about how to come up with the best process."

Once qualified, the HRPP coordinators are also appointed as IRB members, so when the meeting concerns a minor revision to an expedited or full board study, the HRPP coordinator qualifies as one board member who can review the revision. This improves the IRB's workflow, reducing the number of revisions that need to be viewed by the full board or sent out to faculty members of the board.

The IRB collects metrics on how long each of the in-person meetings last, and most seem to last 15-20 minutes. This partly is because researchers are asked to respond to questions in advance, Coleman explains.

"For example, in the case of stipulation notices, we ask researchers to submit a draft response the day before the meeting, and then we've already devoted approximately a half-hour to our pre-review, so we know what needs to happen," she says. "We know what changes need to be made and we go through each item, and can say, 'On line four of page five, this is where you need to make a change.'"

HRPP coordinators also have readily available template language that researchers, who bring their laptops to the meetings, can use as needed.

"Now that all of our coordinators are board members, our goal is to do some sort of process for expedited reviews, as well," Coleman says. "An initial meeting for an expedited review might take longer than 30 minutes."

The meetings make the coordinators' daily work more efficient, and studies move through the review process faster, Coleman notes.

"Before, I'd see an exempt study back and forth, and now it sits on my desk until the 30-minute meeting, and then it's done," she says. "Since we have that dedicated time, we can go through them quickly, spending less time on them overall."

The in-person meetings will continue regardless of how the federal regulations change, Coleman says.

"Depending on the final rule, and our institutional policies, the meetings might evolve into more education than addressing our requested revisions," she suggests. "We can use these to help researchers learn more about the regulations."

Some of the 30 minutes already is used for educational purposes, which was one of the goals when the program began, she notes. ■

IRB Manager Offers Tips on Improving Office Operations

Try this strategy to improve workflow

The work pace is speeding up, and it's not just IRBs — although IRB directors are noticing the effect of having more demands on existing staff. This is a challenge IRB managers can meet by improving their office workflow and operational efficiency.

"One of our challenges involves the increase of volume of work with everyone wanting output quicker and quicker," says **Rebecca Banchik**, CIP, manager of the IRB at Icahn School of Medicine at Mount Sinai in New York City.

Banchik's office handled the workflow pressure through operational changes, some of which worked and others that needed to be tweaked.

"Our office tried to distribute incoming work to staff without losing quality," Banchik says. "We tried, and it failed, becoming an administrative nightmare to assign all incoming work on a daily, rolling basis."

Each day, the IRB office assigned work to employees, asking them to complete those tasks by the end of the day. It didn't work and only added administrative stress and burden to the team, Banchik says.

The chief problem was that there was no way for staff to predict which days would have heavy loads and which would have light loads, and this made it difficult for them to prioritize their efforts. So the IRB kept the same intent of scheduling work for office staff, but distributed work on a weekly basis instead of daily basis, Banchik says.

"We found it worked much better when it was implemented as a weekly deadline schedule," she says. "Every Friday, our office has a deadline that tells the research community when their project should be expected to go to the board, and they're on a routine schedule."

IRB staff can plan their submissions and help their team plan and prioritize their work. "On Mondays, we reassign the work to the analyst, depending on what teams they're on," Banchik says. "They get their work for the week, rather than on a daily basis, and they can plan it out rather than have every morning be a complete surprise."

Having a weekly schedule improved staff satisfaction and productivity, she adds.

To make the weekly schedule efficient without workflow bottlenecks, the IRB advised study teams and investigators of the change and suggested that rather than rushing to submit less well-prepared applications by Monday, they should take a few extra days to make them better and submit on Thursdays, Banchik says.

"We think it's much better communication, and everyone is clear on what our schedule is," she explains. "There are flexibilities and ways to put people at the front of the line if a high-priority item is happening."

Another IRB office efficiency change involved the office's central review process, which has been underway for the past year and a half.

"Our team structure includes IRB associates, who do first-line administrative support to the team," Banchik says. "There are IRB analysts who do regulatory pre-reviews and manage projects with board members."

Banchik views the IRB associates as the review process bouncers. They have the authority to reject incomplete submissions, send a letter to the study team outlining which information is missing, and explain how they can resubmit once the application is complete.

Once all basic information is in place, it proceeds to the IRB analyst who conducts a complete review of the study.

"This process increases the IRB's overall [efficiency] metrics and turnaround time because no submissions are accepted unless certain administrative processes or criteria have been completed," she says.

Once an analyst has reviewed the project, it can be seen by official IRB reviewers, who determine whether the study needs a full board or expedited review. Expedited reviews are seen by a designated member of the IRB, including Banchik and other staff members who are appointed to the board.

"Because we have an organized structure and schedule, the IRB associates know where to go to get their projects for the day," Banchik says. "They know where the projects end up going once they're either accepted or rejected, and the analysts know what is expected of them."

The IRB's workflow also is

enhanced by the IRB's policy to rely only on general boards, rather than specific department IRBs, she notes.

"We have a general board that can see a project from any department," she says. "The reason I think that's a good thing is because it doesn't cause a time delay when you have to send it to a specific board that has a specialty focus."

Review time bottlenecks occur when projects are delayed while waiting for a specific board to have room on the agenda, Banchik adds.

The IRB learned this the hard way when trying out a specialized oncology board and finding that projects had increasingly long waits. The specialized board model also led to more chaotic scheduling for IRB analysts, she says.

The general boards have specialists who are members, and if they are missing a particular specialist or expertise, they can call for someone from the outside to help with the review, Banchik says.

Another workflow best practice is the IRB's deferrable issues process.

"We meet with our chair before every board meeting to review issues raised by the board reviewers, and we provide the opportunity to the study team to address those issues prior to the actual meeting," Banchik says. "This helps reduce our deferral rate, so more studies are approved than deferred to another meeting."

The process works by giving researchers the opportunity to address issues raised by board members prior to the review meeting.

When board members raise a question about a study, the IRB lets the study team know that a particular issue was raised and tells them they can answer those questions prior to the full board review, Banchik explains.

This helps investigators get their study submissions into better shape and improves the chances of a project being approved. "We've gotten great feedback on this," Banchik says. ■

Longstanding Sex Bias in Clinical Research Still a Problem

Not breaking results down by sex could mask adverse reactions

Echoing historical trends, researchers have found that a significant level of sex bias exists in human surgical studies. Though women and men are being included in roughly equal numbers in some papers, only about one-third of the articles reviewed for a new study[1] reported the data by sex, and even less than that analyzed the data independently for men and women.

"Sex bias exists in human surgical clinical research," concluded researchers led by **Melina R. Kibbe**, MD, a clinician in the department of surgery at the University of North Carolina at Chapel Hill. "Few studies included men and women equally, less than one-third performed data analysis by sex, and there was wide variation in inclusion and matching of the sexes among the specialties and the journals reviewed. Because clinical research is the foundation for evidence-based medicine, it is imperative that this disparity be addressed so that therapies benefit both sexes."

Furthermore, the sex of the participants included in the research was not stated at all in 17.3% of the studies, the researchers found.

"If research is conducted on both sexes, but the results or outcomes of the drug are reported in aggregate with the response in both sexes lumped together, how will we know if a drug has a different effect in one sex over the other?" Kibbe tells *IRB Advisor*. "If we are ever to achieve true precision medicine, we must address the basic variable of sex first."

For example, the human papillomavirus vaccine is much more effective in women than men, she says. However, if sex-based reporting of the data was not done, the poor efficacy in men may have diluted the overall results to the degree that vaccine development may have been abandoned.

"We need to have bigger studies so the results in men or women are not diluted," says **Julie A. Freischlag**, MD, a clinician at the University of California-Davis Health System, who co-wrote an accompanying commentary[2] on the study. "If gender is specified, investigators may see results skew higher or lower for a specific sex, which could help create targeted therapies for one sex or, conversely, offer caution around certain therapies."

The roots of the problem go back to 1977, when the FDA cited a lack of safety data in recommending that women of childbearing age be excluded from clinical trials. Even as the safety of including women in trials

became more established, other issues contributed to a continuing historical bias in clinical trials.

"For many years, some diseases, such as heart disease and lung cancer, were thought to only be male diseases, so women were largely left out of studies," Freischlag says. "Now, of course, we recognize that coronary heart disease is the number-one killer of both men and women, and that about a quarter of women in the United States will die from heart disease. In addition, the female menstrual cycle has been perceived by some to be a complicating factor for studies, making it 'easier' to enroll men."

As a result, the National Institutes of Health "Revitalization Act" in 1993 called for inclusion of women in clinical research funded by the NIH. However, Kibbe and colleagues found that the problem persists.

"The FDA has no mandates or requirements for sex-based reporting of the data with new drug applications," says Kibbe. "Given the lack of policy, focus, or requirements by any funding or government agency, these data did not surprise me."

The research blind spot could mean drugs much more effective in men may be ultimately recommended for women as well, creating the disturbing possibility of more side effects and adverse outcomes in women because they were underrepresented in research populations.

"For example, the odds of an adverse drug reaction in women is 50% greater than in men, women are more likely to be hospitalized because of an adverse drug reaction, and 80% of the drugs removed from the market by the FDA are because of undesirable adverse effects in women,"[3-5] the researchers report.

Collecting data on both male and female participants and conducting an independent analysis by sex could reduce this problem and lead to better treatment for men and women.

"Unless a study is focusing on a disease specific to only women, such as uterine or ovarian cancer, we should include both genders," Freischlag says. "One of the bigger points here is around harm prevention. Some therapies that work well in men may actually be harmful to women, causing unnecessary suffering and possibly death. By identifying both men and women in studies, potential harmful effects could be mitigated. I don't recommend a 50-50 mandate, but I do recommend enrolling all who sign up, regardless of gender, and reporting both sexes in studies."

The researchers gleaned data from five surgery journals, analyzing studies published from Jan. 1, 2011, through Dec. 31, 2012. Of 1,303 articles reviewed, 17 (1.3%) included males only; 41 (3.1%) included females only, and 1,020 (78.3%) included males and females. However, 225 studies did not report the sex of the participants.

"Regardless of good overall inclusion of females in human surgical clinical research, we were surprised at the low rate of matching of participants regarding sex," Kibbe and colleagues noted in the paper. "Furthermore, we were amazed that the sex of the participants included was still not reported in more than 17.3% of peer-reviewed studies."

Overall, only 23% of the articles included a discussion of sex-based results.

"Sex matching of the included participants in the research overall was poor, with 45.2% (589 of 1,303) of the studies matching the inclusion of both sexes by 50%," the researchers reported. "During analysis of the different surgical specialties, a wide variation in sex-based inclusion, matching, and data reporting existed, with colorectal surgery having the best matching of male and female participants and cardiac surgery having the worst."

The authors note that to their knowledge, the study is the largest and most comprehensive paper to examine sex bias in human surgical clinical research.

Kibbe and colleagues recommended that FDA mandate that drugs and devices be tested equally in male and female participants before approval. In addition, they called for journal editors to require authors to report the sex of all participants studied and perform sex-based analysis of the data.

"This is a simple thing to do — it just takes doing it," Kibbe says. "The FDA is a bigger issue. To require testing in both sexes, have it powered appropriately, and require sex-based reporting of the data can be done. I am not sure why the FDA has not done this, but the more we raise awareness of this important issue, I am hopeful for change." ■

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Federal Marijuana Decision a Buzzkill for Researchers

In what was widely viewed as a blow to expanding marijuana research for such conditions as post-traumatic stress disorder (PTSD), the U.S. Drug Enforcement Administration (DEA) recently rejected a petition to reclassify cannabis from its current status as a Schedule I drug.

Cannabis remains in the DEA's most restrictive category along with heroin and LSD, despite the arguments of researchers that it is a safe and effective treatment for PTSD, and various forms of pain relief and oncology therapy.

"Using established scientific standards that are consistent with that same FDA drug approval process and based on the FDA's scientific and medical evaluation, as well as the legal standards in the CSA, marijuana will remain a Schedule I controlled substance," the DEA announced in a letter to the petitioners.[1] "It does not have a currently accepted medical use in treatment in the United States, there is a lack of accepted safety for its use under medical supervision, and it has a high potential for abuse. If the scientific understanding about marijuana changes — and it could change — then the decision could change."

The DEA has five drug categories, with the remainder going from Schedule II (i.e., cocaine, oxycodone) down to Schedule V (cough preparations and analgesics). Though there has been a lot of research with medical marijuana, advocates of rescheduling the drug say the current classification hinders establishing large clinical trials that could demonstrate efficacy and remove the "no accepted medical use" label. The result is a classic catch-22, as research advocates note that "the federal government has made it virtually impossible for researchers to study the therapeutic efficacy of cannabis."[2]

One of the petitioners who requested the DEA reclassify cannabis said he will appeal the decision.

"I had expected potentially that they would move it to Schedule 2, but even that is not considered appropriate placement," says **Bryan A. Krumm**, MSN, RN, CNP, BC, a psychiatric nurse practitioner at Sage Neuroscience Center in Albuquerque, NM. "Keeping it in Schedule I only strengthens my argument with the Court of Appeals that this administrative process is futile. I argue that it is the states, not the federal government, that should make the determination of what is accepted medical use. [The DEA] is overstepping their bounds in making this determination when 25 states have accepted medical use of cannabis."

Krumm recently published a paper[3] citing a "broad range of therapeutic effects seen in treating PTSD with cannabis," while underscoring the alarming number of suicides in veterans with the condition. Given its effect on the "underlying neurobiological processes that are involved in PTSD, cannabis is so much more effective than pharmaceuticals for treating PTSD," he tells *IRB Advisor*.

Despite its refusal to reclassify the drug, the DEA letter states that it will continue to support marijuana research. "For instance, DEA has never denied an application from a researcher to use lawfully produced marijuana in a study determined by the Department of Health and Human Services (HHS) to be scientifically meritorious," the agency stated. ■

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Language Creep and Informed Consent: When Did 'Human Experiments' Become 'Clinical Trials?'

Surprisingly, not in immediate aftermath of Nuremberg Trials

There was a time when research involving human subjects was not couched in the relatively innocuous terms like "clinical trials" or "research," but labeled baldly as an "experiment."

While on the one hand a seeming innocuous matter of semantics, there is also the concern that the development of more euphemistic phrasing for human research is a subtle erosion of informed consent.

"'The point of using the term

'study' or 'clinical trial' is to put a positive spin on the whole enterprise," says **Carl Elliott**, MD, a professor in the Center for Bioethics at the University of Minnesota. "People are afraid if they hear the phrase 'human experimentation.' It has become so associated with the abuses of the past it could scare people off. If it's a question of informed consent, maybe they should be scared off."

Elliott gave this matter some thought and penned a recently published essay on the subject, recalling the time an attorney speaking to an audience involved in various aspects of human research said, "Don't call it a study. Don't call it a clinical trial. Call it what it is. It's an experiment."[1]

The common perception may be that the notion of "human experiments" was convicted and exiled from research language at Nuremberg during the Nazi war trials.

"No, it wasn't Nuremberg," he says. "In fact, it wasn't even the big scandals of the 60s and 70s here like Tuskegee and Willowbrook [State School in Staten Island, NY]. It took a while after the American scandals for the bad connotations of the word 'experiment' to spread. But it was definitely the case by the mid-1990s."

Specifically, a 1995 survey by federal Advisory Committee on Human Radiation Experiments found that "medical study" was perceived by patients as a much less risky endeavor than participating in a "medical experiment."[2] Some people viewed the term as the final option of terminally ill patients, Elliott notes.

"The shift from the term 'experiment' to 'clinical trial' and 'research study' is really just a small part of the whole change of language in research," he tells *IRB Advisor*. "It is all about keeping information away from patients. Ironically, if you look at informed consent documents, the language is so clinical and so bureaucratic that you can't imagine a research subject reading that and getting the full emotional impact of what they are signing up for. The documents read like indemnification clauses or the fine print in a rental car agreement."

As part of this shift in nomenclature, controversial and unethical research began to be described as the Tuskegee syphilis "experiment" or the Stanford prison "experiment."

"If you are a researcher, recruitment is a huge problem, so surely you are not going to use any language that is going to possibly scare people off," Elliott says. "So it doesn't surprise me at all the researchers would shy away from using words like 'experiment.' But it is a little more striking that supposed neutral fields like bioethics or federal guidelines have all gone along completely with this shift. Even codes of research like the Declaration of Helsinki have gradually cleansed themselves of the word 'experiment.'"

Of course, there is no shortage of examples about of using cloaked language in other areas of medicine, few more brazen than the CDC's original use of the arcane word "nosocomial" to describe infections acquired by patients in a hospital. The CDC was concerned that hospitals wouldn't report what are now called healthcare-associated infections if they more directly described an adverse event that has implications for liability.

"'Clinical trial' is a term that the general public does not understand at all," Elliott says. "For you and me it becomes completely normal to use that term, but in the real world nobody knows what a clinical trial is. When you use that phrase instead of the word 'experiment' — a word which people do understand — it does seem like an intentional effort to confuse people." ■

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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.

COMING IN FUTURE MONTHS

- Advancing health literacy in informed consent
- Bioethics trends in pharma
- Best practices in preparing for a site visit
- Improving violations submissions

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. Scan the QR code to the right or log on to AHCMedia.com, then select "MyAHC" 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. In May 2014, the European Union published what regulation involving clinical trial results?

A. The European Clinical Trial Regulation (EU No. 536/2014) explains new requirements for authorizing, conducting, reporting, and providing transparency in all clinical trials that have at least one EU member site.
B. The EU research regulation gives researchers and sponsors permission to return individual research subjects' personal health findings to them during a clinical trial.
C. An EU clinical trial regulation authorizes a fine to sponsors and investigators who fail to return generalized study results to subjects within six months of the close of a clinical trial.
D. All of the above

2. In a study of Zika virus in U.S. Olympic athletes, coaches, and staff, comparative research will be conducted for those who:

A. participate in indoor versus outdoor events.
B. have symptomatic versus asymptomatic infection.
C. recall mosquito bites versus those who do not.
D. all of the above.

3. When an IRB office moves to improve workflow and efficiency, why might a weekly schedule work better than a daily one, according to Rebecca Banchik, CIP?

A. IRB employees are less likely to call in sick if on a weekly schedule.
B. Daily schedules take a great deal more work to establish and require 24/7 attention from managers.
C. On a daily schedule, there is no way for staff to predict which days would have heavy or light loads, and this made it difficult for them to prioritize their efforts; on weekly schedule they can more easily adjust work priorities.
D. Most electronic calendars work better in a weekly mode.

4. To researchers' surprise, how many of 1,303 articles reviewed did not report the sex of participants?

A. 140
B. 78
C. 350
D. 225