IRB ADVISOR

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INSIDE

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COVID-19 Trial Protocol/Consent Issues Discussed on National Stage

Placebo vs. access to the available vaccine

By Sue Coons

Few modern clinical research trials have been followed by the public as closely as the current COVID-19 vaccine studies. It should be no surprise that nationwide media reports have focused on and debated the trials' protocols and informed consent processes.

On Dec. 2, a World Health Organization (WHO) ad hoc expert group published an editorial in the *New England Journal of Medicine* about why placebo-controlled trials of COVID-19 vaccines are still needed — even as the vaccine is rolled out to the public.[1] "While vaccine supplies are limited, available vaccines are still investigational, or public health recommendations to use those vaccines have not been made, we believe it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo," the group wrote. "Moreover, under these conditions, we believe that trial sponsors are not ethically obligated to unblind treatment assignments for participants who desire to obtain a different investigational vaccine."

> "THIS OPPORTUNITY TO OBTAIN RELIABLE EVIDENCE ABOUT LONGER-TERM EFFECTS WOULD BE DESTROYED BY EARLY UNBLINDING AND IMMEDIATE VACCINATION OF PARTICIPANTS ASSIGNED TO PLACEBO."

The last statement started an ethics debate on the social media platform

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Twitter, in which the question of how ethical this approach is, unless it is spelled out clearly in the informed consent. Several people who said they were participants in a COVID-19 trial chimed in and said they had not been informed of this. To note, the language in their informed consents was not provided.

"This opportunity to obtain reliable evidence about longer-term effects would be destroyed by early unblinding and immediate vaccination of participants assigned to placebo," the WHO ad hoc group wrote. "Although each participant has the option to pursue any available intervention, if substantial numbers of participants choose not to do so, continuation of blinded follow-up in a population in which no licensed vaccine is being deployed could yield important and unexpected findings that would be difficult to obtain reliably any other way."

On Dec. 2, *The New York Times* (*NYT*) quoted a married couple in a vaccine study who thought they would receive the vaccine as soon as it was shown to be safe and effective.[2] The wife said she received a modified consent in November that indicated people in the placebo arm of the trial may have to wait up to two years to receive the vaccine, "if they get one at all." The woman told the NYT that she was "owed" that vaccine.

Ethics During a Pandemic

Pfizer issued a statement in October that it would vaccinate the placebo arm of its trial. "If Pfizer's vaccine is granted emergency use authorization, we would propose to amend our ongoing study to allow crossover of eligible placebo subjects to the active vaccine arm if they wish to do so at any time. The statistical considerations and details regarding the appropriate protocol language, informed consent, and logistics of this process would need to be carefully developed together with the regulatory authority."[3]

"There are always potential ethical issues and spillover effects when you are talking about conducting clinical trials on vaccines in the middle of a pandemic," says **Tim K. Mackey**, MAS, PhD, associate professor at the University of California San Diego, and Director of Healthcare Research and Policy at UCSD - Extension. "First among them is the fact that study participants who are not receiving the intervention (in the control arm) may drop out of the trial when a vaccine begins to become available to the public, either through another vaccine candidate approval or based on a shorter study, etc." This could lead to dropout as participants do not know if they are in the control or treatment arm, he says. In addition, participants who have consented still may choose the security of knowing if they were vaccinated.

"I also think that it is possible that a study participant could try to procure access to a vaccine (such as another candidate that has been approved) while in a study," Mackey says. "Then, they would typically not meet the inclusion criteria for the trial anymore, though it would depend on the study." Or, the participant could take a drug or other product as a preventive prophylaxis, which could affect study participation. An example of this would be the misinformation around hydroxychloroquine.

"It is really important to keep in mind that the point of trials is to determine whether a new vaccine confers a benefit of protection and

to build a profile of its side effects, if any," says **Alex John London**, PhD, director of the Center for Ethics and Policy at Carnegie Mellon University in Pittsburgh. "Safety data is particularly important in the case of a vaccine since vaccines are delivered to 'healthy' people. I put [healthy] in quotes since although these people aren't sick with the disease in question, they may have a wide range of underlying medical conditions. One of the things we want to find out is whether there are people with particular medical conditions that experience more severe side effects than others."

If participants seek the vaccine on their own outside the trial, that can have important consequences for their own health and for the integrity of the study. "While they are blinded, participants don't necessarily know which intervention they received. If they received the vaccine, then getting vaccinated again would consume a scarce resource unnecessarily and expose the person to unknown risks of taking two vaccines," London says.

Part of the point of the two arms is to compare the rate of various problems in those who received the investigational vaccine and those who did not, London says. "If trial participants seek the vaccine on their own, it detracts from the trial's ability to estimate how many adverse events would have happened anyway and how many might be due to the vaccine."

Informing About Adverse Effects

Experiences with high fevers and other adverse effects in vaccine trials also are hitting the national media. One nurse who said she worked in research wrote an account in the *Journal of the American Medical Association* about experiencing a 104.9°F fever after receiving a second injection in a trial.[4] In addition to the fever, she felt light-headed, chilled, nauseous, and had a "splitting" headache. "The adverse effects of the vaccine — even if, at worst, they all happen at once — are transient and a normal sign of reactogenicity, signaling an effective immune response," she wrote. However, the author said that despite the "extensive information she had on the research process and vaccine," she was unprepared. "[O]n a personal level, I did not get the message that I should anticipate a reactogenic response." She is concerned that other patients will not get the message that adverse effects with the vaccine show that the vaccine is working.

"In the context of potential adverse events, I would imagine that is sufficiently covered in the IC [informed consent], though I think there are more proactive means of administering IC in the context of a public health emergency, such as providing additional information about possible vaccine misinformation or how to respond to potential media reports about a vaccines' safety profile — perhaps reiterating the role of the [The Data and Safety Monitoring Board] and IRB for patient safety, that need to be given more attention," Mackey says. "I also think that there could be special protocols for more dynamic consent management and reconsent, not just as a trial progresses and more data become available, but ultimately as the pandemic progresses and conditions change on the ground — risk of infection, number of cases, availability of other treatments, etc."

One of the challenges of IC is to communicate the relevant uncertainties to participants in terms they will understand, London says. "It is very important that we do not foster the 'therapeutic misconception,' which is the perception that study participation entails access to validated medical treatment. In the case of novel mRNA [messenger RNA] vaccines, I think it is also important to make sure that participants understand that the reason the trial is slated to last for two years is because it is important that we have a clear picture of the safety of the vaccine in a large and diverse population."

However, even in the best case, it would not be surprising if the participants did not remember all the information given to them during the consent process. "It's also difficult to anticipate at the start of the trial when results will be available since a lot depends on where the studies are carried out and the transmission rates in those places," London says.

If the public health response had been better, the estimates of efficacy might be delayed. "As it is, because COVID-19 is basically out of control at the moment, they're able to see enough cases to estimate efficacy fairly quickly," London adds. "Now we find ourselves in a position in which we have very promising estimates of efficacy fairly early on in the anticipated life of the trial."

Study participants certainly have a right to be updated on the new information that has come from the trial they are in and all study participants are free to withdraw at any time. "I think they should be encouraged to remain in the trial because of the importance of generating a clear picture of the side effect profile of a novel vaccine, using a novel strategy, " London says. "If it is permissible to ask the public to wait while early doses are provided to healthcare workers or people

at elevated risk, then I think it is permissible to ask study participants to remain in the trial. It is never permissible to force people to remain in a trial." ■

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20 Years of Reports on Research Protection

Board members offer a look back and ahead

By Melinda Young

Editor's note: *IRB Advisor* was first published in 2001, a couple of years after research participant Jesse Gelsinger died during a gene therapy clinical trial. Shortly after Gelsinger's death, the federal government began to increase oversight of human research studies. To commemorate the past 20 years of human research protection, as well as two decades of *IRB Advisor*, we asked editorial advisory board members to comment on how things have changed since 2001.

Kay Ball, PhD, RN, CNOR, CMLSO, FAAN, adjunct professor, nursing, Otterbein University, Westerville, OH, has been on the newsletter's editorial advisory board since 2001.

James Riddle, MCSE, CIP, CPIA, CRQM, vice president, research services and strategic consulting, Advarra, Columbia, MD, is a current editorial advisory board member.

Below are the questions and answers, which have been edited for length and clarity.

IRB Advisor: *What do you believe are the biggest changes IRBs have experienced over the past two decades, and how well has the industry handled this change?*

Ball: One of the biggest changes is the increase in research — the number of research projects assigned to nursing students working on advanced degrees and the ability of IRBs to handle this increased workload. For some, wait times for IRB approvals have decreased when more professionals have been added to handle this extra workload.

IRBs exist to protect human rights, but sometimes bureaucratic procedures for this protection have slowed the progress of research. IRBs are continually working to solve this problem.

IRBs also have worked diligently to maintain ethical, regulatory, and scientific goals for protecting human subjects over the years. In addition, IRBs review more potential research that involves multiple sites and even include international sites within the same research project. If an IRB has enough members who represent diverse backgrounds (ethics, science, research), then the IRB is able to handle the increase in workload properly.

Riddle: I'm not fond of the term "industry" when we describe IRBs. I prefer the word "community," and view IRBs and organizations that administer them as part of the research community facilitating and advancing research in collaboration with researchers.

The biggest change over the last two decades is consolidation of the independent IRB community. Twenty years ago, there were lots of smaller independent IRBs. Now, there are two large IRBs and several other smaller independent IRBs. We can be better partners with the community and with researchers when we have more resources available to us. We can offer more support and services and help facilitate the research more.

New private research sites and institutions do not have to use as many different IRBs as they used in the past.

Over the last 20 years, there has been a recognition that a centralized IRB is OK and is good for the overall community. Many people have accepted that having more ethics committees review the same protocol does not necessarily produce a better

protocol. That idea has manifested in guidance and regulation. You see the National Institutes of Health mandating a single IRB in multicenter studies, and the new Common Rule requires single IRBs. Those regulatory changes have been building up for the last 20 years.

IRB Advisor: *When* IRB Advisor *was first published, research programs were still dealing with the fallout from Jesse Gelsinger's death (1999) during a gene therapy clinical trial. Then, in 2001, Ellen Roche, a young lab technician died after participating in a clinical trial for treating asthma.* IRB Advisor *provided analysis of the implications of these tragedies in its first year of covering human research protection. Now, looking back at these incidents, how do you believe the IRB and human research protection world has evolved and changed in response to those deaths?*

Riddle: Even the terminology of research protection has changed. In the late 1990s and early 2000s, the primary focus was on compliance of the IRB — the oversight committee. Reviewing the facts of the Gelsinger and Roche tragedies reveals multiple failures, throughout the institutions, that led to their deaths. Yes, there were IRB issues, but there also were other issues related to what was going on at the institutions that were beyond the IRB's scope.

The biggest thing that has happened in response to the deaths has been this transformation from focusing just on compliance of IRBs to creation of overall human research protection programs at universities or institutions conducting the research. The Roche and Gelsinger deaths were tragic, and out of that tragedy came a betterment of the overall human research protection program.

Ball: The IRB and human research protection continue to advance, but very slowly. A lot more can be done with IRB oversight of human subjects and determining if the risk to the human is warranted in the study.

IRB Advisor: *What do you see as the biggest challenge IRBs will face over the next two decades, and why?*

Ball: One of the challenges is protection of human subjects, which should be comprehensive but not obstructive to the advancement of the research. Just overseeing studies is a challenge.

Also, it is a challenge to have timely approvals of the exempt studies if the IRB is backlogged with applications for research approvals.

Riddle: There will always be challenges. This past year has shown us that sometimes we do not even see the challenges coming.

If I had to pick the two biggest challenges, they would be, first, determining as a community how to operationalize the logistics of doing a single IRB. The Common Rule mandate to do a single IRB is only a [couple of years] old. The NIH policy for mandating single IRBs has only been around for a few years. Institutionally based IRBs — academic or health system — have not yet figured out how to efficiently operate a single or central IRB. Independent IRBs have been operating as single IRBs for 30-plus years and have perfected intricate and expensive computer systems and work flows to facilitate the logistics of handling many research protocols with hundreds of performance sites.

I still hear from my academic friends that institutional-based IRBs continue to struggle with the logistics of five- or 10-site studies. Over the next decade, we'll see a continued shift and recognize that companies that administer IRBs have the resources to be able to do the single IRB more efficiently, handling the logistics of recordkeeping and document distribution as well as other logistical issues that go into a single IRB.

I am not talking about the ethics portion of the single IRB. By and large, we all do a good job of reviewing the ethics of the studies. Instead, I am referring to the logistics of managing multiple sites. The biggest challenge for academic IRBs is to handle the logistics of managing a single IRB. At some point, they'll just get tired of doing it, or they'll come to the realization that there are private companies that have already figured out how to do it.

The second and equally challenging issue for the IRB community is the transition from a traditional protocol to more virtual protocol technologies. We see this with COVID-19 and teleconferences instead of onsite visits, and remote monitoring. Researchers can use Google glasses to see what is going on in participants' homes. For example, a participant cannot go to see the researcher. A home health nurse can go to the home and wear Google glasses to observe the participant do their walk test or determine if they are having a drug reaction. This is super cool technology.

My point is that in relation to the IRB community, that will change the way IRBs think about design of protocols and change the IRB's approach and evaluation of risk in protocols. We have to be ready as a community for that shift.

Over the next two decades, virtual trial technologies and logistical challenges of the single IRB will be the biggest challenges we'll see.

IRB Advisor: *As someone who has worked in healthcare, research, and/or human research protection and been an editorial advisory board member for* IRB Advisor *since its first issue, what*

do you know about the human research enterprise now that you wish you had known in 2001?

Ball: I wish I would have known more about how closely human subjects are monitored in research studies. Are the risks to the humans in line with the goals of the research or usefulness of the data collected? Also, I would have liked to know more about the details of the definition and/or requirements of an exempt study when involved with nursing student applications. ■

OHRP Looks Back at its First 20 Years

By Sue Coons

Editor's note: In its inaugural issue in April 2001, *IRB Advisor* featured a story about the creation of the Office for Human Research Protections (OHRP), formerly the Office of Protections from Research Risks (OPRR). *IRB Advisor* asked OHRP to look back since its launch in June 2000 to see how human research protections has evolved. OHRP requested that its answers be attributed to an "OHRP spokesperson."

A Time of Scrutiny

"OHRP was founded at a time when its predecessor office (OPRR) was under considerable scrutiny due to a series of widely publicized compliance actions against a number of large, prestigious academic research institutions, which involved temporary suspensions of those institutions' research programs," OHRP says. "While the rationale for creating OHRP was to move the office outside of the authority of NIH [the National Institutes of Health], many people believed that the creation of OHRP was intended to revise the relationship between the federal government and the regulated institutions to promote a more collaborative relationship."

OPRR was created in 1972 and fell under the NIH. When its replacement, OHRP, was established on June 13, 2000, the agency moved under the Department of Health and Human Services' (HHS) Office of the Assistant Secretary for Health. OHRP was designed to lead the HHS efforts "to protect human subjects in biomedical and behavioral research and to provide leadership for all federal agencies that conduct or support human subjects research under the Federal Policy for the Protection of Human Subjects, also known as the Common Rule."[1]

David Satcher, MD, PhD, who was then assistant secretary, said that OHRP's long-term goal was to develop "new, stronger, and clearer patient protection policies, with an expanded focus on performance and prevention."[2] The organizational change was intended to allow effective coordination across HHS and provide a model for other federally and privately sponsored research, he said.

The switch to OHRP came after the September 1999 death of volunteer Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania. In May 1999, the U.S. government had temporarily shut down the license to conduct human research at Duke University Medical Center after investigators said the university could not ensure the safety of trial participants. Duke blamed the lapses on "administrative" issues.[3] Within a year, federal investigators had halted all or some research at seven other institutions.

In 1998, the Office of the Inspector General (OIG) of HHS also published its report, *Institutional Review Boards: A Time for Reform*, which described IRBs being overwhelmed with demands that put their effectiveness in jeopardy.[4] The report blamed scarce resources as a primary problem. An update to the report was published in April

2000. It reported expanded federal enforcement efforts but little other progress in any of the first report's recommendations.[5]

"In the last decades of the 20th century, the human research subjects protections system in the United States was very de-centralized," OHRP says. "Most research studies were conducted by single research institutions, and the regulations delegated the responsibility for human research subject protections to the institutions conducting the research. The federal office overseeing the regulations was quite small, and its auditing capacity was quite limited. This meant that the quality of compliance with the regulations was very much institution-specific. There is very little research or other information documenting the quality of research protections provided during those years."

Scientific Advances in Research

Much has changed in scientific research since then. "Over the last 20 years, scientific advances, especially in the areas of genetic research and information technology, the increased availability of large data sets and stored biospecimens, and the integration of research into the delivery of clinical care, have contributed to changes in the human research protections system," OHRP says. "In addition, the rise in multisite research and the role of nontraditional research sites such as community healthcare clinics, corresponded with a growth in independent IRBs and institutions' reliance on IRBs operated by outside organizations.

"Perhaps not coincidently," OHRP says, "this was also the period when the human research protection field became more professionalized. In 2001, the Association for the Accreditation of Human Research Protection Programs, Inc. [AAHRPP] was founded, and institutions began to seek voluntary accreditation. And in 1999, Public Responsibility in Medicine and Research [PRIM&R] began offering the Certified IRB Professional certification for individuals working with IRBs."

AAHRPP currently lists 257 organizations on its website with full or qualified accreditation, while PRIM&R says more than 3,000 individuals have been certified since it was introduced.

One big change happened with the revision of the Common Rule, which went into effect on July 19, 2018. Changes to the rule included:

- new and revised definitions for such terms as "human subject," identifiable biospecimen," and "clinical trial";
- new categories of secondary research exempt from the Common Rule;
- elimination of continuing review for minimal risk studies;
- revised informed consent requirements.[6]

The revised Common Rule recognized that technology has had an impact on the nature of research by including several new provisions that were designed to address this change, OHRP says. "For example, technological advances have led to a rise in secondary research using 'big data' and biospecimens left over from clinical procedures, which has the potential benefit of learning from large numbers of research subjects, while avoiding the physical risks posed by some interventional studies.

"To address this change and more appropriately calibrate the research protections required for such secondary research, which mainly pose informational risks to subjects, the revised Common Rule includes several new exemptions that incorporate privacy and confidentiality protections, and in some cases a new option for broad consent, but do not impose all of the same requirements that apply to higher risk interventional studies," OHRP says.

Some in the research community wished for more guidance from OHRP and IRBs after the revision. For example, the revised Common Rule required informed consent forms to be organized and easier to understand for participants but did not specify on how to make that possible. As of 2019, OHRP has not offered guidance on the revisions, said **Joy Jurnack**, RN, CCRC, CIP, FACRP, in an opinion piece for the Association of Clinical Research Professionals. "IRBs want to honor the revisions and will assist the research team, but it is up to the team to complete whatever template the IRB supplies with the details required to comply with the Common Rule. IRBs will assist and edit, but the initial work is on the research team."[7]

The COVID-19 Challenge

As soon as it became clear that COVID-19 was a serious and highly transmissible infection, OHRP says it began working with the Office for the Assistant Secretary of Health and its federal partners, including the Food and Drug Administration and the Centers for Disease Control and Prevention, to develop guidance that would help the research community manage and protect research participants during the pandemic.

OHRP published its guidance in response to the coronavirus for

research regulated under 45 CFR part 46 on April 8, 2020. On April 28, OHRP held a live webcast to explain the guidance and answered questions from the research community. The guidance document, the archived video of the webcast, and other related resources that could help inform the research community on protecting research participants during the pandemic are available on the OHRP website (https://bit.ly/3mo4Gy3). OHRP also says it has been working closely with the team of public health and communication experts across HHS to promote the use of the resources on the About Research Participation (https://bit.ly/3gSGHpf) website to help combat the "fear, confusion, and misinformation about research and research participation in the public."

Some of the changes that IRBs have made to research protocols from the COVID-19 guidance may remain after the days of the pandemic have passed. A May 2020 survey of clinical research professionals at the UT Southwestern Medical Center in Dallas showed a positive reaction to trial modifications, such as telehealth appointments and allowing electronic signatures. Survey respondents said that the changes positively affected patient safety; treatment efficacy; patient and staff experience; and communication with patients, investigators, and sponsors.[8] More than 90% of respondents, especially those with the more professional research experience, thought some of these COVID-19-related clinical research adjustments should continue after the pandemic ends. ■

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Data Safety Monitoring Boards Were Quietly Behind the Scenes, but No More

Media talks about DSMBs and vaccine trials

By Melinda Young

The year of the coronavirus pandemic has ushered in a time when the quiet, behind-the-scenes work of data safety monitoring boards (DSMBs) has entered national consciousness.

"The pandemic has brought DSMBs into the limelight. They were always important, but a quiet part of clinical trials; now, CNN and CBS News try to explain their role to the public," said **Jonathan Seltzer**, MD, MBA, MA, FACC, chief scientific officer at WCG in Philadelphia. Seltzer spoke at a Dec. 2 WCG webinar on COVID-19 research.

DSMBs have been an essential fabric of clinical trials in recent decades, but until 2020, their work largely was under the public radar. When interim information came out about a few vaccines for SARS-CoV-2, this all changed. Television, newspaper, and online journalists began to talk about DSMBs and their role in pausing studies and watching for safety issues.

"It's amazing to get people to understand DSMBs and that they're now mainstream," says **Mitchell Warren**, executive director of AVAC, a global HIV prevention organization in New York. Warren is on a DSMB for HIV research as an advocate member. "Now, my mother knows about stopping clinical trials. As her

son, who has been working on this for years, I don't think she knew about DSMBs before COVID," Warren says. "COVID has opened up opportunities to explain research. It has changed the conversation."

The DSMB, as defined by the Department of Health and Human Services (HHS), is "a committee of experts responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of study subjects and validity and integrity of the data."[1]

In November, DSMBs monitoring the Pfizer/BioNTech coronavirus vaccine and the MODERNA mRNA-1273 vaccine candidate found positive interim results in how the two products prevented SARS-CoV-2 infection.[2] The National Institutes of Health (NIH) reported on Nov. 16 that an independent DSMB found the NIH-Moderna vaccine to be safe and effective for adults.[3]

DSMB members are independent experts who have no vested interest in a specific treatment, according to the HHS Office of Inspector General (OIG), in a 2013 report, titled *Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance, But Facing Some Issues*.

DSMBs meet regularly to review interim trial data. If they find issues related to safety or data integrity, they can make a recommendation about whether the clinical trial should continue or be stopped.[4]

In the 2013 report, the OIG found that four of seven trials the DSMBs recommended stopping were based on findings that the treatment was ineffective. The other three were based on the trials' problems with enrolling enough research participants in the allotted time necessary for useful results.

Recent DSMB recommendations with the Pfizer and Moderna vaccine candidates were to make the study intervention more widely available because of its efficacy.

"Rapid evaluation of vaccine therapy has allowed manufacturers to move toward an emergency use authorization [EUA]," Seltzer says. "If they show a modicum of success, we'd like to end those trials so people can avail themselves of those therapies."

"DSMB FOLKS NEED TO UNDERSTAND THE IMPACT OF THEIR DECISIONS AND HAVE A GOOD DEAL OF COMFORT WITH THE UNCERTAINTY OF EVALUATING CLINICAL TRIAL DATA."

DSMBs need several characteristics to succeed at these data reviews. First, they must be independent. Members cannot have any personal or academic interest in the trial they evaluate, he says.

"That's harder than you might think, especially in a highly politicized environment," Seltzer explains. "DSMB folks need to understand the impact of their decisions and have a good deal of comfort with the uncertainty of evaluating clinical trial data."

This is especially true during the pandemic, when DSMBs must avoid public perceptions of political or financial influence over their decisions. They also must be vigilant to view data more often in case of safety or efficacy concerns.

"As we look back at 2020, the public might see the traditional role of data safety monitoring boards, and this has forced DSMBs to be more responsive and faster acting than ever," Seltzer adds. "I hope these changes to DSMBs will endure and be a silver lining at the end of [the pandemic]."

To a DSMB, safety is the primary focus: "Every conversation begins with, 'Is it safe?'" Warren says. "Even if a product is effective, the board spends an inordinate amount of time to see if it's safe."

Warren says DSMBs review studies at various points in clinical research, assessing study design, and asking these sorts of questions:

- Are there specific issues?
- Is there a clear analysis plan?
- Are there clear stopping rules?

"There can be hundreds of pages of data tables, safety events, and anything that has occurred, including diarrhea, nausea," Warren says. "The frequency of DSMB meetings depends on the clinical trial."

Members of DSMBs should reflect all aspects of a clinical trial, he says.

"Clinical trials need statistics, medical professionals, an ethicist, and someone who represents the community that will be impacted by the trial," Warren explains. "Their independence is fiercely protected."

For instance, one DSMB member stepped off the board when her employer began to fund a trial that was related to — but not the same as — the one the DSMB was monitoring, he recalls.

"Most DSMB meetings are boring. They look at data and see if the product looks safe," Warren says. "They want stringent data to show

benefit, and if you stop for efficacy, it's hard to do; stopping for harm is much more focused." ■

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DSMBs Have Helped Advance Safe, Effective HIV/AIDS Research

Circumcision trials are one example

By Melinda Young

Data safety monitoring boards (DSMBs) have played a big role in helping the most effective and safe HIV therapies advance.

In 2020, lost amidst the news of the coronavirus vaccine trials, there were some amazing news in HIV prevention — thanks to DSMB work, says **Mitchell Warren**, executive director of AVAC, a global HIV prevention organization in New York.

A pre-exposure prophylaxis (PrEP) trial, with a bimonthly injectable intervention, had excellent efficacy data. So a DSMB recommended stopping randomization in the large trials, Warren explains.

The injectable was incredibly effective, and the DSMB recommended that everyone be told that it worked better than the PrEP pill to which it was compared, he adds.

"So, they were told both products worked, and they had to choose which one to use, but the trial didn't stop because there still was a lot of safety data the board wanted," Warren says.

The interim results, reviewed by the DSMB in May found that the PrEP regimen with long-acting cabotegravir (CAB LA) injected once every eight weeks was superior to daily oral tenofovir/emtricitabine (TDF/FTC) for HIV prevention.[1]

Then, on Nov. 9, a PrEP regimen containing cabotegravir injected every eight weeks in women from southern and east Africa also worked well at preventing HIV infection. The injectable PrEP had superior efficacy to Truvada at preventing HIV. The DSMB found no safety concerns and recommended that the National Institute of Allergy and Infectious Diseases stop the blinded phase of the trial, which originally was set to continue until 2022, and share the results.[2]

From the perspective of people at risk of HIV infection, this early clinical trial news means there soon might be a drug that can be injected just every other month and it will be more effective than taking a daily PrEP pill.

"Even though we got excited about the news of the women's trial, it came out on Nov. 9 — the same day Pfizer put out its first data about the coronavirus vaccine," Warren says. "If that had not happened, this would have been front-page news."

DSMBs sometimes have to stop trials when the study product does not work well. They also might stop trials of interventions that work better than anticipated.

For example, the circumcision trials, performed in South Africa, Kenya, and Uganda about 15 years ago, showed high levels of safety and efficacy. Men who were circumcised as part of the clinical trial had significantly fewer HIV infections. The interim research showed a protective rate of at least 60% among circumcised male participants who had sex with women.[3]

The DSMB found that the circumcision intervention was ethical and safe, and the DSMB wanted to look at interim data more frequently, Warren says.

"Then, nine months later, the DSMB saw data from both trials and said it is time to stop the trial," he explains. "The DSMB said it was unethical to continue the trials because these two trials showed that

circumcision is a safe and effective tool."

In 2007, the World Health Organization began to recommend circumcision programs at least two years before the trials had been scheduled to end, Warren says.[4]

By 2018, more than 18 million men in priority countries had been medically circumcised as part of the voluntary medical male circumcision program.[5]

These trials and the DSMB's intervention before they ended demonstrate the importance of having independent boards review interim results, Warren notes.

"When you are looking for efficacy, you want very solid data," he adds. "When it comes to harm, even some slight serious harm is enough to stop a trial."

There also have been HIV intervention trials in which the studies were stopped because the DSMB found in checking interim data that the active product arm had an infection rate similar to placebo. The DSMB said it was not ethical, nor a good use of resources, to continue the trials as there was no hope the product would show benefit, Warren explains.

A Ghana microbicide trial, called SAVVY, had drastically lower HIV incidence rates than what statisticians had expected when the trial was designed, showing that participants were benefiting from prevention messages and services. The trial would be unable to answer the question of whether the microbicide worked, and the DSMB recommended the trial be stopped.[6]

DSMBs sometimes halt trials because of potential harm to participants. For instance, two clinical trials in Africa of a vaginal microbicide, Ushercell, were halted in 2007 because an interim data review from one of the trials suggested a possible increased risk of HIV infection among female participants.[6]

"HIV has been at the front end of a lot of DSMB innovations," Warren says. "With HIV in the 1980s, we began to see an engagement of communities pushing for involvement in research and designing protocols."

Having an advocate like Warren on a DSMB was pioneered by the HIV community.

> "WHEN YOU ARE LOOKING FOR EFFICACY, YOU WANT VERY SOLID DATA. WHEN IT COMES TO HARM, EVEN SOME SLIGHT SERIOUS HARM IS ENOUGH TO STOP A TRIAL."

"Developing trust in the research process and research enterprise is really challenging," Warren says.

Including advocates on a DSMB is a way to involve the affected community in research and build trust and confidence, he adds.

"Those pauses by DSMBs give us confidence that there is someone looking at safety, not just researchers moving ahead," Warren says. "DSMBs monitor safety of people in trials, and they also help people gain confidence in the research enterprise, and that's critically important today — more than ever." ■

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CME/CE QUESTIONS

1. **How can COVID-19 trial participants severely damage the integrity of their study?**

   a. Drop out before the trial ends to ensure they receive the vaccine.
   b. Compare experiences with other participants to see if they received the vaccine.
   c. Receive the vaccine or take a preventive prophylaxis from outside the study.
   d. Complain to media sources about their experiences in the trial.

2. **According to Mitchell Warren, a DSMB member, and executive director of AVAC, a global HIV prevention organization, which is the primary focus of every data safety monitoring board?**

   a. Is the study drug effective?
   b. Is the study intervention safe?
   c. Is the trial ethical, equitable, and fair?
   d. Is documentation following human research protection regulations?

3. **What did the human research protections landscape look like when OHRP was created in June 2000?**

   a. Academic research institutions had fewer safety and compliance violations.
   b. Most institutions handled their own research protection oversight.
   c. IRBs had more available resources during that time.
   d. Its predecessor OPRR fell under the guidance of HHS' Office of the Assistant Secretary for Health.

4. **According to an Office of Inspector General 2013 report about data safety monitoring boards, which qualities are important for DSMB members to have?**

   a. They are doctorate-level scientists and physicians.
   b. They represent rival study treatments.
   c. They are independent experts with no vested interest in a specific treatment.
   d. They are researchers, statisticians, and medical professionals.