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INSIDE



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# Study of COVID-19 Vaccine in Pregnant People 'Too Late'

*Financial and public relations risks are obstacles to their inclusion*

*By Sue Coons, MA*

On Feb. 18, Pfizer and BioNTech announced they would dose about 4,000 healthy pregnant women with the COVID-19 vaccine to evaluate its safety, tolerability, and immunogenicity. In media statements, the companies said that since the vaccine campaigns initially had been successful, it was time to extend the clinical program to other vulnerable populations, such as pregnant women.[1]

Women's health advocates and researchers disagree with the timing of the study. "From my perspective, it's too late. Pregnant women are not being studied soon enough. We need to devote more of our public and scientific attention to this group," says **Kristina Adams Waldorf**, MD, researcher and professor of obstetrics and gynecology at the University of Washington. "The drug companies should have studied the vaccine in pregnant women from the very beginning. We now have more than 30,000 pregnant people in the United States who were vaccinated for COVID-19. As we expected, we have not seen any significant outcomes on the pregnancy or the neonate, which is in line with what we know about the biology. Why couldn't we offer pregnant women the same reassurance that we did other adults regarding safety and efficacy?"

> "PREGNANT WOMEN ARE NOT BEING STUDIED SOON ENOUGH. WE NEED TO DEVOTE MORE OF OUR PUBLIC AND SCIENTIFIC ATTENTION TO THIS GROUP."

Although pregnant people were excluded initially from the COVD-19 trials, research has shown they are at higher risk for more severe disease. A study of pregnant patients with SARS-CoV-2 infections in Washington state between



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March 1, 2020, and June 30, 2020, revealed a fourteenfold increase in case-fatality rates than that of similarly aged people with COVID-19. In fact, pregnant women represented "nearly 10% of SARS-CoV-2 deaths among 20- to 39-year-olds in Washington state."[2] Most patients with SARS-CoV-2 in pregnancy experienced mild disease and recovered, the researchers said. However, one in 11 developed severe or critical disease, one in 10 were hospitalized specifically for a COVID-19 concern, one in 30 were admitted to the ICU for respiratory concerns, one in 60 were mechanically ventilated, and one in 80 died.

The research team also published results showing the SARS-CoV-2 infection rate in pregnant patients was 70% higher than similarly aged adults in Washington state.[3] There also was a twofold to fourfold higher prevalence of pregnant patients with COVID-19 infections from communities of color than expected based on the race-ethnicity distribution of pregnant women in Washington in 2018.

"Even when we removed all of the pregnant women that we identified at the time of labor and delivery who were asymptomatic, we still had a 30% higher infection rate in pregnant people," says Adams Waldorf, the senior author of the study. "We don't know if that's because they have larger households, if they have children in day care, or if they themselves are essential workers. Lots of my pregnant patients are working to help support their families in healthcare, teaching, and in elder care facilities."

## Fear of Risks

A week before the Pfizer/BioNTech announcement, National Institutes of Health (NIH) officials published an article stating pregnant and lactating people should have been included in the original COVID-19 vaccine trials. "Long-standing obstacles" to the inclusion of these people exist in clinical research, wrote **Diana W. Bianchi**, MD, director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and colleagues.[4]

According to information provided by the manufacturers in the emergency use authorizations, pregnant people were excluded in the trials for both the Pfizer and Moderna vaccines. In addition, the data from women who did become pregnant during the trial have provided "limited data to inform evidence of safety and effectiveness in this population." Some preclinical rodent data were included from the Moderna trial, the authors noted, but did not take place early enough to support the inclusion of pregnant patients in the trial.

"Efforts by the Centers for Disease Control and Prevention through its V-Safe registry as well as industry and the Food and Drug Administration will yield postmarket vaccine surveillance information from pregnant people, including evidence on the effects of the vaccine on pregnancy and infant outcomes," they wrote. "These data will be useful, but in the meantime, pregnant people and their clinicians must make real-time decisions based on little or no scientific evidence."

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) made recommendations on how to improve the inclusion of pregnant and lactating people in clinical research. Even so, ethical and liability concerns remain barriers to this type of research, the authors wrote.

The PRGLAC authors proposed additional protections for these people through rulemaking and government initiatives that can reduce liability.

A pregnant person should have the same evidence about a vaccine that is provided to other individuals, the authors noted. "The information that pregnant and lactating people need to make this decision should be tailored to their individual risks based on potential exposures in their home and work environments, their medical comorbidities, and their demographic characteristics, combined with the evidence on the safety and effectiveness of the vaccine and its potential effects on a fetus. Pregnant and lactating persons should not be protected from participating in research, but rather should be protected through research."

**Pamela Payne**, BSN, MSN, NP, a maternal-infant nursing instructor at the Patricia A. Chin School of Nursing at California State University in Los Angeles, says the Pfizer/BioNTech clinical vaccine trial with pregnant women is important — and she wishes that it had been part of the initial clinical trials.

"Pharmaceutical companies are very reluctant to include pregnant women in clinical trials because they worry about the financial and public relations risks should the vaccine or medication prove deleterious to the fetus or the newborn," she says. "IRBs are tasked with protection of research participants, so they, too, have been reluctant to include pregnant women in clinical trials. Yet this pandemic is of such grave proportions, and the risk of coronavirus infection to pregnant women is so significant, a carefully designed trial should have been earlier on the company's radar."

Safety measures can be put into place for this type of trial, she says. "Requiring closer monitoring of pregnant participants in the trial by the safety review board is a way to ensure that any potential adverse effect is being recognized early and evaluated for the possibility of an early end to the trial, should an adverse effect be serious enough to warrant it."

Adams Waldorf believes there has been a reckoning in science, medicine, and in society to recognize vulnerable and marginalized groups better than in the past, including pregnant people and underrepresented minorities. NIH has put rules in place to ensure women and children are studied more, instead of just the default of white men. "Pregnant women are now being recognized as an important group based on their vulnerability to COVID-19. But, scientifically, when they were not studied in the early vaccine trials, they were essentially marginalized," she explains. "We have enough preclinical data and data from animal models to have very solid scientific evidence that we don't think that there will be complications. Excluding pregnant people from the vaccine trials was a mistake."

> "PREGNANT AND LACTATING PERSONS SHOULD NOT BE PROTECTED FROM PARTICIPATING IN RESEARCH, BUT RATHER SHOULD BE PROTECTED THROUGH RESEARCH."

The American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and others have been pushing for inclusion of pregnant people. "Fortunately, they were not excluded from receiving the vaccine, but it's not enough. We need to do more," Adams Waldorf states.

## Evaluating the Trial

Pfizer/BioNTech's Phase II/III trial is a randomized, placebo-controlled, observer-blind study. It will include women age 18 years and older and between 24 to 34 weeks of gestation. According to the study details, each woman will participate for approximately seven to 10 months, depending on whether she receives the vaccine or placebo. The infants will be monitored through approximately six months of age. The researchers will study safety in infants of vaccinated pregnant women and if the infants received antibodies from the mothers. After a participant's child is born, participants will be unblinded, and those who were in the placebo group will receive the vaccine.[1]

"We should be studying women who are getting the vaccine in all trimesters, and following up the infant as well. That's standard practice," says Adams Waldorf. "The gold standard is to study all trimesters and to follow the infant up typically for a few years."

Studying women in the 24-34 week gestation window and following up with newborns certainly is a reasonable accommodation to the risk/benefit profile, Payne says. "Given the critical development of organ systems in the first trimester, it is reasonable to wait until later second trimester to avoid impact on those critical stages. Ideally, should

the vaccine prove safe and efficacious in the gestational period under study, results could be carefully reviewed for likelihood of safety and efficacy in earlier gestational periods."

The trial authors also did not mention an effort to recruit minority participants, even though people of color often experience more severe COVID-19 infection. Payne says she is disappointed to hear that no specific mention of participant diversity was given. "It may be that the company is attempting to have a diverse group and it is important to have that data, given the greater impact that the disease is having in minority populations," she says. "However, trying to recruit minority participants faces a barrier of suspicion due to historically egregious medical research protocols conducted in these communities, as well as the general societal reluctance to risk the health of a pregnant woman and her fetus. I would hope to see a diverse population, but the knowledge gleaned from the trial is still of such critical need that I would hesitate to criticize the trial solely for a lack of diversity. If minority communities are not currently included, I would hope that the company would design a diverse trial as soon as possible."

## Informing Future Trials

Even with its late start date, the Pfizer/BioNTech vaccine trial in pregnant woman will contribute important data, the researchers say. Every clinical trial with pregnant women, undertaken with careful evaluation of the potential for risks, and with close monitoring of participants throughout the trial, is valuable to reassuring researchers that it is possible to include pregnant women in trials more routinely.

"I am not advocating for future testing of any and every new medication on pregnant women," Payne says. "However, vaccines or medications that could potentially ameliorate known significant, serious health risks to pregnant women and their fetuses must be studied during pregnancy to provide women and their clinicians the knowledge with which to answer questions of safety and efficacy. I would hope that this vaccine trial will help this goal."

The studies now will help to inform the next generation of COVID-19 vaccines that might be a little better at covering all the variants, says Adams Waldorf. "All of this research will continue to inform our scientific and medical approach to vaccination in pregnancy." ■

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# United Kingdom Begins First COVID-19 Human Challenge Study

*Bioethicists say much can be learned from the results*

*By Sue Coons, MA*

Lawmakers, academics, and the research community have hotly debated the ethics of a human challenge study (HCS) since the first months of the COVID-19 pandemic. Now that the United Kingdom has started dosing patients in its HCS, some bioethicists say this trial can show vaccine efficacy in ways the larger vaccine trials cannot.

The U.K. human challenge study will expose healthy volunteers, ages 18 to 34 years, to the COVID-19 virus in a controlled environment. Organizers of the trial say it will help show the effect of the virus on the volunteers as well as identify which vaccines seem to be the most effective.

This HCS may answer questions left unanswered by the large vaccine trials, says **Arthur L. Caplan**, PhD, director of the division of medical ethics at New York University Langone Medical Center and School of Medicine. The large trials that opened the door for emergency use authorization from the FDA are experiencing issues with participants wanting to drop out. Some patients want to make sure they are vaccinated, but unblinding them affects the long-term data. Caplan does not see many people wanting to sign up for new trials for vaccines in the pipeline, either.

"Yet we have questions to ask about which vaccine is better, which lasts longer, which prevents transmission, which does better against new variants, which is cheaper," he says. "There are a lot of questions that we are still going to want to know the answers to. I think challenge studies could get us to the answer quickly, and they may be the only way in reasonable periods of time to get answers."

The timing of these trials is not ideal, says **Seema K. Shah**, JD, a lawyer and medical ethicist at Northwestern University Feinberg School of Medicine. "If early vaccine studies hadn't been able to complete enrollment, that could have been a good reason to do challenge trials. Alternatively, once vaccines are widely available and it becomes more difficult to test new versions of vaccines because placebo controls are not ethically acceptable, there might be good reason to prioritize vaccine candidates by comparing them in challenge trials. These trials are also testing the old strain of the novel coronavirus, and not the newer variants. Nevertheless, they may identify a correlate of protection (a measure of when people are protected from infection or disease) or develop insights into disease or transmission that are valuable."

In the longer term, challenge trials to develop a universal coronavirus vaccine might be really useful, Shah says. "Challenge studies involving people who have previously had COVID-19 are a safer option that may produce similar insights, so I wonder why those are not happening first."

At the beginning of the COVID-19 pandemic, lawmakers, health researchers, and advocates sent letters to U.S. government agencies asking them to consider human challenge studies for COVID-19 development.[1] The first letter in April 2020 was sent by 35 members of the House of Representatives to Alex M. Azar, JD, then secretary of the Department of Health and Human Services (HHS), and Stephen Hahn, MD, then commissioner of the U.S. Food and Drug Administration (FDA). The representatives encouraged the agencies to consider human challenge trials.

On July 15, 2020, the organization 1Day Sooner, which advocates for people seeking to participate in high-impact medical trials, wrote an open letter to Francis Collins, MD, PhD, director of the National Institutes of Health (NIH). The letter was signed by 177 Nobel Laureates, experts, and academics urging the U.S. government to consider human challenge or controlled infection trials. "If challenge trials can safely and effectively speed the vaccine development process, there is a formidable presumption in favor of their use, which would require a very compelling ethical justification to overcome," they wrote. The letter also spelled out several protections that could be put into place for an effective COVID-19 human challenge trial.[2]

In its guidance, titled Development and Licensure of Vaccines to Prevent COVID-19, published on June 20, 2020, FDA responded with this: "If it is no longer possible to demonstrate vaccine effectiveness by way of conducting clinical disease endpoint efficacy studies, the use of

a controlled human infection model to obtain evidence to support vaccine efficacy may be considered. However, many issues, including logistical, human subject protection, ethical, and scientific issues, would need to be satisfactorily addressed. At this time, no controlled human infection models for SARS-CoV-2 have been established or characterized."[3]

In a letter dated June 30, 2020, **Anthony S. Fauci**, MD, director of the National Institute of Allergy and Infectious Diseases, responded to the consumer advocacy organization Public Citizen, based in Washington, DC. "Controlled human infection (CHI) studies are one research approach that might help determine the effectiveness of a vaccine," Fauci wrote. "However, the best way to determine both safety and efficacy is through the current plan of conducting adequately powered, randomized, controlled trials. I agree that CHI studies can raise significant ethical questions, and it is important that these questions be examined and carefully considered prior to undertaking such studies. If the randomized controlled trials prove infeasible for any reason, CHI studies, if able to be conducted safely and ethically, could be an important and scientifically sound complementary strategy to more traditional vaccine development approaches."[4]

The chief compliance officer of one of the nation's largest providers of regulatory and ethical review services spoke about the issues IRBs would experience with human challenge trials. "IRBs would be very reluctant to approve a trial without some kind of mitigation (such as using a weakened strain or a population unlikely to have severe reactions) to protect the safety of subjects," said **David Forster**, JD, MA, CIP.[5]

Researchers also published responses to the debate, including one from November that called human challenge studies "unethical" at that point. "We think proponents' core claim about speeding vaccine development is flawed, and we believe that the risk-benefit balance for such HCS is both too uncertain and likely to be unacceptable, even with greater information," the researchers wrote. "In addition, issues of resource allocation are critically important and difficult to justify. Vaccine trials aiming to undertake risky and uncertain steps in human subject research — particularly those that depart from standard approaches to protection of subjects in HCS — risk further exacerbating increasing levels of public mistrust related to SARS-CoV-2 vaccine development. Taken together, we believe that these arguments make undertaking SARS-CoV-2 HCS both unwarranted and unethical. At this critical moment in the response to the pandemic, it would do more harm than good."[6]

> "IT IS TRUE THAT IN SOME WAYS, CHALLENGE TRIALS ARE LESS URGENT NOW THAT VACCINES HAVE BEEN FOUND SAFE AND EFFICACIOUS. BUT IN OTHER WAYS, CHALLENGE TRIALS HAVE NEVER BEEN AS URGENT."

**Nir Eyal**, DPhil, director of the Rutgers Center for Population-Level Bioethics, published a paper in March 2020 with two epidemiologist colleagues about how HCS could be used to accelerate coronavirus vaccine licensure.[7] In January, Eyal, Caplan, and legendary vaccinologist Stanley Plotkin, MD, published an opinion update, stating HCS should still be considered.

"It is true that in some ways, challenge trials are less urgent now that vaccines have been found safe and efficacious," Eyal wrote. "But in other ways, challenge trials have never been as urgent."[8] Eyal and colleagues argued that challenge trials could:

- determine the efficacy of vaccines in preventing infection;
- determine whether vaccines prevent mucosal infection;
- measure the comparative efficacy of different vaccines in these two roles;
- measure the comparative efficacy of regimens for vaccines (e.g., half-dose, spaced out);
- determine vaccine efficacy against new viral variants;
- determine the correlates of vaccine protection to assess efficacy in different populations;
- quickly triage for unpromising next-generation vaccine candidates;
- determine the duration of immunity by challenging participants months after they receive the vaccine;
- determine the quality and duration of post-natural infection immunity by challenging people previously infected with COVID-19;
- help test therapeutics.

"Multiple vaccines for SARS-CoV-2 have proven highly efficacious in preventing disease," the authors concluded. "Global health requires testing both these and further vaccines in the critical additional role of blocking infections, and in defining the correlates and duration of vaccine protection. Large, randomized field trials

comparing vaccines to controls have now become much harder to perform. Yet human challenge studies, such as the ones that the U.K. is planning, can and should play an important role in the necessary investigations we still have to carry out."

Critics of the HCS say it is too risky for the participants. Caplan believes the risk benefit is reasonable, about the same faced in a kidney donation. COVID-19 treatments are improving, he says, and researchers can develop a dose that produces biological changes without symptoms.

The risks still are fairly uncertain. "I worry about the risks of long-term symptoms from COVID-19 infection or an unexpected death among the participants, and the risks to society of a study like this, especially if it has negative outcomes, increasing distrust in vaccines or vaccine hesitancy," Shah says. "Given that the social value of these trials is not very high or clear, I think it is a close call about whether these studies are justified."

Another question is how to ensure the trial participants give fully informed consent. "Part of what we need to verify is that the participants know that only a bit is known about some of the risks and potential complications of long COVID," Eyal says. "A fairly distinctive aspect is that the 'right answer' to some questions should be 'I don't know, and nor do you.' But that's not entirely unique. There are often deep unknowns in medical trials. In fact, in the recent field trials for COVID vaccines, there were many such unknowns about the product used. It was the first time that these vaccines were tested in humans, and some of them were from a wholly new family of vaccines."

Also, what is appropriate compensation for a patient who is deliberately exposed to a virus? Adequate compensation depends on the time they will spend in the study and the burdens they take on, Shah says. "I think the best way to address and minimize risk is not to give them money up front but to make sure they receive prompt, free treatment if they end up being harmed."

Caplan says he also would argue against compensation. Instead, they should be altruistic volunteers. "I don't want the issue of money mixing or confusing with the question of motivation."

The U.K. trial can help set up the speed of HCS trials in the future, Caplan says. It would help the process to go faster, he explains, if researchers already knew how to trigger challenge studies at a particular isolated location. They should also maintain a registry of people who are willing to participate.

Caplan says he is seeing less resistance to the idea of a HCS than when he spoke about it in April 2020, especially since the large trials are not always possible to complete. "I think there's been some shift in thinking now that people see what the impact is on existing trials." ■

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# IRBs, Researchers Starting to Recognize Security Breaches of Online Survey Data

*Fixing problem is laborious*

*By Melinda Young*

The creators of an online survey, designed to explore breast cancer and reconstruction among African American women, began enrolling participants slowly. Surveys trickled in, accumulating 30 completed surveys over several weeks. Suddenly, the survey rose in popularity. Within two days, more than 80 completed surveys came in.

"I immediately knew what was happening, and shut down the survey," says **Lorraine R. Reitzel**, PhD, FAAHB, FSRNT, IRB chair and professor at the University of Houston. Marketing for the survey had not changed, so investigators knew it could not have recruited so many new, eligible participants that quickly.

Another sign that something was wrong with the completed surveys was the timing in which were submitted. Batches of surveys arrived in two-minute intervals, says **Shahnjayla K. Connors**, PhD, MPH, CPH, assistant professor of health and behavioral science in the department of social sciences at the University of Houston-Downtown.

Other signs of a breach included suspicious responses, unusual email addresses and patterns, responses from outside the United States, and missing contact information.[1]

## Incentives Attract Bots, Scammers

Connors and Reitzel believed the survey had been breached. One possible cause was the way investigators marketed the survey. A link went out to groups connected to breast cancer survivors — but anyone could share the survey link, and they probably shared it with the wrong people.

Another factor was the $20 Amazon gift card investigators offered participants as an incentive for their time completing the survey. "We sent the gift cards electronically," Connors says.

That small incentive was enough to attract electronic bots, which are software programs that can execute commands and perform routine tasks. The fact the surveys were dropped two minutes apart, and some were blank or did not include contact information, suggested they were not filled out by a person.

"We had to go through every single survey; it was pretty labor intensive," Connors explains. "At first, I had to look for things that didn't look right, something in the diagnosis, or something like they said they made $80,000 a year, but had Medicaid insurance."

If any red flags arise, the researchers put the survey in a separate pile.

Connors began the laborious work of verifying each survey. She called the numbers they provided to see if the number was connected to a woman. In some cases, the numbers were disconnected or were attached to a doctor's office or another random place.

"We sent each woman an email, saying that we looked at their application and needed further review and would they mind contacting us," Connors says.

Several people responded with anger, saying the researchers were running a scam and that they had put in their time and wanted their gift card, she recalls. Two people went through the additional verification and were shown to have completed legitimate surveys, but the rest were likely fake.

Connors was determined to fix the breach and ensure the only survey data collected would be from eligible participants. This study was important to her, personally, and to the body of knowledge about Black women and breast cancer.

"Particularly for women of color, there's not a lot of research out there, and I wanted my data to be valid, useful, and meaningful," Connors says. "Otherwise, it defeats the purpose."

## Ensure Data Integrity

As the breast cancer reconstruction survey continued, researchers asked potential participants to contact a member of the research staff. "Then, we created an individualized survey link for that person," Reitzel says. "We thought bots were less likely to reach out to the investigator to get a link."

While this created another barrier between participants and research staff, it was an effective step toward ensuring data integrity. "We did not reach the target of 100 breast cancer survivors, but we reached 59 people

in the end, when funding was over," Reitzel says. "The extent to which we were hampered is unknown."

## Issue Is Widespread

Shortly before the study enrollment was breached, Reitzel heard a cautionary tale from a colleague about seeing surveys churning out every couple of hours. Something had changed in the enrollment, and it was not because investigators had changed their recruitment strategy or tapped into a new well of potential participants.

"As she described this issue with her study, I started asking her questions," Reitzel says. "I asked if she had alerted the NIH [National Institutes of Health] and the IRB."

In these breached survey studies, the earliest surveys were returned by the people targeted in recruitment. But there was evidence the later rush of completed surveys was completed by electronic bots or people who did not meet the study's enrollment criteria.

"They wonder why they're getting this large input of people when, really, they should have only 30 participants or some smaller numbers in chunks of time, depending on how they're rolling out their marketing," says **Danielle A. Griffin**, EdD, CIP, associate director of research integrity and oversight at the University of Houston.

Griffin and Reitzel learned increasing numbers of investigators were experiencing similar issues. "In our compliance office, we learned this had happened to even more people," Reitzel says. "All these students, doing student research, trying to get through their dissertations and theses, and when their surveys are breached, they're probably very excited about making their survey numbers."

Unfortunately, what looks like good news actually is a mess they will have to clean up. They may never learn exactly what was behind the breach, although incentive payments are the most likely explanation.

Even studies designed to recruit students and offering course credit as incentive might be hacked, Griffin notes. Many universities use cloud-based participant management software to recruit students for studies and to offer them course credit. "We've had reports, and one was through a whistleblower, who knew their friend hacked the system and completed a survey twice so they could get additional credit," Griffin says. "This student sent an anonymous email, saying, 'Hey, you may want to check this data because I know my friend hacked the system and completed the survey and put in garbage data' — not exact words, but a heads-up."

Many researchers rely on these platforms and expect students to complete the survey at no cost to investigators so they are collecting data for free. "But how many are hacking it? Hopefully, it's a small number, but if they were able to do that for one survey, then they could do it for others," Griffin says. "This just questions the reliability of the data."

Breached surveys disrupt research and turn a fairly straightforward electronic process into one that requires much more time than expected. "First, they have to go through all of the surveys to weed out the ones that are valid," Griffin says.

Sometimes, it requires investigators to perform additional research, such as contacting participants with new questions. Researchers may have to email all participants and ask them to take an additional step, such as calling into the research office, before they can receive their incentive payment. There may be no response from the false surveys, but the participants who meet the criteria may respond emotionally to the added inconvenience.

"They might be upset you're withholding their money because they didn't see the email asking them to call in, and so they didn't send in a response," Griffin says. "You'll have participant complaints."

In one breached study, it took several months for the valid participants to receive their incentive payment. This can affect relationships and trust with a community investigators may want to work with during future studies.

## Verify Each Survey

If researchers are not cautious in verifying each completed survey, they run the risk of harming their data integrity with bad data. When researchers suspect a survey breach, they should contact appropriate regulatory entities, including NIH (if applicable) and the IRB.

The IRB asked Reitzel and Connors to show how they could protect the study's integrity — and participants — as the study continued. *(See story on preventing survey security breaches in this issue.)*

"Lorraine and I came up with a plan, moving forward, of having women contact us first," Connors says. "Before, we had a survey link on the flyer. I think that was what the issue was because we distributed it to breast cancer groups, and once it goes out you don't know where it goes."

After the breach, they removed the link from the flyer and required women who were interested in

participating to contact investigators for more information. When they called, Connors verified they met eligibility for the study and sent them a personalized link to the survey.

Each participant received a separate link so it could not be shared with other people.

"Of course, nothing is 100%," Connors says. "But we didn't have any issues after sending out that link." ■

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# Take Steps to Prevent Damaging Security Breaches in Survey Studies

*By Melinda Young*

IRBs can help investigators create a plan to prevent survey security breaches that can lead to false data and study slowdowns and shutdowns.

"Most of the breaches we've seen have been in relation to how they're recruiting in paid marketing mechanisms, like paid Facebook or Google ads, and the link to the survey is being distributed inappropriately," says **Danielle A. Griffin**, EdD, CIP, associate director of research integrity and oversight at the University of Houston. "The wrong people are accessing the survey."

## Ensure Researchers Report Breaches

The first question could be whether investigators were identifying and reporting a breach to the IRB. "A lot of investigators come to the IRB for help because they don't know how to deal with it," she says. "But some investigators may handle it and not report it to the IRB."

IRBs should ensure researchers know that if they detect a breach that changes/corrupts data, leads to someone outside the research team accessing data, causes potential harm to participants, or requires a change in procedures or informed consent, it should be reported to the IRB.

## Create a Survey Security Plan

Researchers can prevent survey hacking issues by creating a thorough plan for preventing and identify security breaches. IRBs can ask researchers:

- How are you targeting study participants?
- Where are you targeting messages to find participants?
- Are there sufficient inclusion criteria and screening questions?
- Do you perform an extra check during the survey and after completion?
- Once someone completes the survey, do you send another link to verify the person is real?
- Will you check participants' email addresses to identify patterns of multiple, similar, or same email addresses?
- If you are targeting one gender in the survey, do participants' names suggest someone of another gender has completed the survey?

Some investigators will offer a drawing for survey participants. This type of incentive may not attract breaches. But, it also could reduce the number of participants enrolling in surveys requiring more time answering questions, says **Lorraine R. Reitzel**, PhD, FAAHB, FSRNT, IRB chair and professor at the University of Houston.

"Eliminating the incentive would eliminate potential motivation to be fake," Reitzel explains. "However, we often get grants where there are incentives built in. This is the way we know how to do it as researchers to get the most people interested in completing your study."

The COVID-19 pandemic has led to more online research work, including virtual meetings and participant interviews. This has opened it to breaches, says **Shahnjayla K. Connors**, PhD, MPH, CPH, assistant professor of health and behavioral science at the University of Houston-Downtown.

"The challenge, as we get digital and focus on Zoom and online work, is there are many more ways to [end up with] fraudulent information," Connors says. For example, virtual meetings between investigators and participants can be hacked, as in Zoom-bombing, she adds.

As more people use these electronic meeting places, the companies are adding more security protections, such as unique links, Connors notes.

Connors, Reitzel, and Griffin offer these additional suggestions for keeping survey studies safe from hacks and data breaches:

• **Prevent bots.** Bots are easy to spot because they often use the same email addresses, locations, and other identifiers.

"Even if you can't verify the first entry, all subsequent entries you can assume are not a human being because of replicate data," Griffin says.

One simple tactic is to add reCAPTCHAs, fraud detection methods that can be as simple as asking someone to check a box that says "I'm not a robot," to requiring people to type in the letters they see, to requiring people click on the traffic lights or crosswalks in a nine or 12-block photo.

"A reCAPTCHA is something we know reduces the chances that someone is putting in fraudulent information," Connors says.

IRBs can request researchers include reCAPTCHAs, Reitzel says.

• **Limit survey participation by location and link.** If researchers plan to only enroll people in a particular state, then it can be set up to receive responses only from individuals in that state. "For national studies, we could exclude people from other countries, but that will not remedy all of our issues," Reitzel says.

Researchers also should send each verified participant a unique link to the survey. This can prevent sharing of the survey link with people who are not eligible for the study and only want to receive the incentive payment.

• **Ask questions with only one answer or open-ended answers.** "We've tried adding an honesty pledge to our survey," Reitzel says.

A survey might ask participants to verify their location, employment, or some other information that pertains to eligibility. If the survey is answered by a bot, it may have both "yes" and "no" answers when everyone who meets eligibility requirements could only answer "yes."

"If it's a bot providing random answers, and if you don't put in 'yes,' then you're taken to the end of the survey," Reitzel explains.

If people are conducting multiple hacks to obtain the incentive payment, they usually do not take time to go through the survey and answer carefully. "At some point, they'll answer something that doesn't make sense," Griffin says. "If it's an open-ended question, the chance of someone thoughtfully answering open-ended questions is less. They'll hack something easier to get through, so having more open-ended questions can be a hard stop."

A similar tactic is to include a question for which the instructions say to mark a particular letter. If either bots or people are randomly entering letter answers, they may miss this instruction. That could mean their survey is discarded.

"Set up the survey so there are validity questions that need to be answered," Griffin suggests. "These are going to be the checks that help determine which survey is real and which is not."

• **Perform random checks.** "Having built-in random checks throughout the study is one of the easiest ways to [prevent breaches]," Griffin says.

"For every survey coming in, I looked at them and made sure they were OK," Connors adds. "Most of the time, you get a couple at a time."

If researchers expect many survey submissions, random checks would help identify breaches and problems. Investigators can inform colleagues of questionable surveys and ask if they also believe a breach occurred. ■

IRB ADVISOR



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# CME/CE QUESTIONS

1. **What do researchers hope to gain from the COVID-19 vaccine trial in pregnant women?**

   a. A look at efficacy through all trimesters of pregnancy
   b. A look at efficacy in minority pregnant women
   c. A way to approach future trials involving pregnant women
   d. A way to involve pregnant women in trials for all new medications

2. **According to some bioethicists, why should human challenge study trials be considered?**

   a. The risk potential is lower than the trials that test vaccine efficacy in unexposed individuals.
   b. Researchers can study vaccine efficacy.
   c. Healthy volunteers would not have long-term reactions to being exposed.
   d. Resources allocation is not an issue.

3. **Which is a practical and effective tactic for preventing a study survey breach, according to Lorraine R. Reitzel, PhD, FAAHB, FSRNT?**

   a. Ask for potential participants to upload a photo ID.
   b. Ask researchers to call each potential participant before sending them a survey link.
   c. Pay a contractor to trace each survey's respondent to verify their location.
   d. Ask questions for which there is only one answer, or open-ended answers.

4. **Which is a sign that a survey study has been breached by internet bots?**

   a. Surveys answers are long and open-ended.
   b. Completed surveys are returned electronically in batches, maybe minutes apart.
   c. A few surveys contain "other" in place of gender.
   d. Email addresses bounce back.