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INSIDE

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Revisiting the 'Unfortunate Experiment' in New Zealand

Surviving faculty member writes book on unethical cancer research

By Gary Evans, Medical Writer

It's astonishing in retrospect — as blatant violations in human research so often are — that women in New Zealand diagnosed with an increasingly clear precursor to cervical cancer were left untreated and uninformed in an unethical study that continued for two decades. Predictably, some of them followed a downward spiral to disease and death in a manner similar to the African-American men with untreated syphilis in the infamous Tuskegee Experiment in the United States.

> THE REPORT CONCLUDED THAT THE EXPERIMENT THAT BEGAN IN 1966 WAS AN EGREGIOUS ETHICAL BREACH BY THE PRINCIPAL INVESTIGATOR AND THE ADMINISTRATION THAT ENABLED HIM.

The so-called "Unfortunate Experiment" at National Women's Hospital in Auckland, NZ, was finally halted after a press exposé[1] in 1987 led to the formation of a board of inquiry that produced a damning report. The Cartwright Report[2] concluded that the experiment that began in 1966 at the hospital was an egregious ethical breach by both the principal investigator and the administration that enabled him. The late gynecologist Herbert Green, MD, began the trial to test his conviction that carcinoma in situ (CIS) was not predictive of progression to invasive cervical cancer. Thus, some women diagnosed with CIS by Green were not treated nor informed about their condition, but rather followed to see if they developed cancer. A disturbing corollary to the main study was that

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Green was found to have performed cervical smears on newborn girls without consent of their parents in an apparent attempt to show that abnormal cell growth was present at birth.

"An analysis of Dr. Green's papers points to misinterpretation or a misunderstanding of some data on his part, and on occasion, manipulation of his own data," the Cartwright Report concluded. "The inference to be drawn from Dr. Green's 1966 proposal and published papers is that CIS will progress to invasive cancer in only a very small proportion of patients, if at all. This inference is incorrect and reliance on it has been dangerous for patients. … It was an attempt to prove a theory that lacked scientific validity and little attention was given to ethical considerations."

Medical staff who cautioned against the trial at the onset or who tried to stop it later were outvoted and essentially ignored by other faculty and administration, who were strangely blind to the ethical lapses and clinical outcomes of the horrific experiment. The board of inquiry found "no reason" for faculty and administration to overlook "basic ethical and scientific information that was then available" as the trial continued.

"The fact that the women did not know they were in a trial, they were not informed that their treatment was not conventional, [and] they received little detail on the nature of their condition, were grave omissions," the board of inquiry reported. "The responsibility for those omissions extend to all those who approved the trial, knew or ought to have known of its mounting consequences and its design faults, and allowed it to continue."

The "failures" cited in the report included that the experiment was counter to generally accepted standards of treatment at the onset, and that it was allowed to continue even as the incidence of invasive cancer rose in the patient population. There was a hierarchical authoritarian work culture that allowed the trial to continue even after dissenting faculty published data on the rising cervical cancer rates of untreated women in 1984.[3]

There appears to be no official agreement on the number of women who died because they were not treated and subsequently developed full-blown cervical cancer. There is no doubt that some died because of the experiment, and 19 patients sued and were compensated in an out-of-court settlement. By the time of the Cartwright inquiry, Green was in his mid-70s and was deemed too ill to be charged. His administrative supervisor was censured and fined by the New Zealand Medical Council.

IRB Advisor asked **Ronald W. Jones**, MD, a retired National Women's OB/GYN faculty member and one of the principal authors of the aforementioned 1984 paper, whether in hindsight he wished he had taken the story directly to the lay press to create the public outcry that eventually halted the trial.

"I have spent much of my life anguishing over this question," says Jones, who has written a book[4] that gives an insider's view of the experiment and the academic culture that allowed it. "I cannot speak on behalf of my two, long-dead colleagues [who tried to stop the experiment]. I came a generation after them and Green's experiment had been underway for seven years when I joined the staff, from England, as a complete outsider,

and I was unaware of it. I was the youngest member of the staff and anxious to establish a permanent contract in the prestigious National Women's Hospital. For some years, I was largely ignorant of the experiment and its evolving outcome."

As it was, Jones claims that he was treated with derision and contempt for publishing the 1984 paper that exposed the ongoing experiment by concluding that the fate of some of the patients showed that "CIS of the cervix had a significant invasive potential." The bitterness of some toward him for exposing the situation has resurfaced again with publication of his book, Jones says.

"Had I gone to the media when we published our [1984] paper I would certainly have been blackballed from my own country," he told *IRB Advisor* in an email interview. "As it was, I became persona non grata soon after the government set up the Committee of Inquiry. Some professional colleagues have refused to speak to me from that time."

Indeed, there are those who have disagreed with aspects of the Cartwright Report and raised questions about whether Green's work was accurately portrayed by critics like Jones.

"The value and strengths of a democratic process are that credible and verifiable opposing opinions should be able to be expressed without prejudice — and be open to public debate. However, in revisiting the Unfortunate Experiment, this is not possible," wrote **Graeme H. Overton**, FRCOG, FRCS, a consultant associated with National Women's Hospital from 1960-1999.[5] "Contrary opinions are not welcome, are seldom printed, and invoke demeaning criticism rather than discussion. In New Zealand, revisiting the Unfortunate Experiment is a minefield inviting self-destruction."

A Cautionary Tale

It has been decades since the study was halted, posing the question whether the Unfortunate Experiment is a historical curiosity or a highly relevant incident germane to the current oversight of IRBs.

"IF YOU TALK TO ANYBODY WHO HAS EVER WORKED IN AN ACADEMIC HEALTH CENTER, THIS SORT OF VERY AUTHORITARIAN, HIERARCHICAL CULTURE IS STILL VERY MUCH INTACT."

"I think everybody should know this story, even beyond IRBs — anyone who is involved in research in any way," says **Carl Elliott**, MD, PhD, a bioethicist at the University of Minnesota. "If you talk to anybody who has ever worked in an academic health center, this sort of very authoritarian, hierarchal culture is still very much intact. The kind of things that Ron Jones describes at National Women's Hospital didn't seem all that unique to me when I was reading them."

That same culture was insular, certainly not conducive to whistleblowers coming out against colleagues, he said.

"The effort to file internal complaints, keep things in-house and within academic medicine did no good," Elliott said. "They could not imagine that this would happen. They assumed that those efforts were going to make a difference. It was not possible for people, [Jones and colleagues thought] to actually see what was going on — that these women were dying — and do nothing about it. Yet, that's what happened."

In the broader context of other human research debacles, the Unfortunate Experiment has really never received widespread attention outside of New Zealand, he says.

"In bioethics in America — and to some extent, the U.K. — there is a sort of standard canon of research disasters that every introductory medical ethics student is taught, starting with Tuskegee, Willowbrook, prison research, and so on," Elliott says. "Nobody seems to pay any attention to this one."

One of the lessons to be learned is that in the wake of the Unfortunate Experiment, New Zealand adopted rigorous and transparent oversight of human research, he adds. This action compares favorably to the more muted response in the U.S. to such incidents, he says.

"They had a disaster on the scale of Tuskegee, but unlike the U.S. they actually tried hard to fix it and they did all these very sensible things," Elliott says. "[These include] a public judiciary inquiry, making the researchers answer for themselves publicly, and they put in an oversight system. And they haven't had anything similar in 30 years. The Cartwright inquiry had a lot of credibility. It was clearly intended to come to a resolution that was

satisfying to the public, the victims, and the people who were afraid that the same thing could happen to them."

While unethical research trials often are exposed and then fade from thought, the experiments of Tuskegee in the U.S. and National Women's in New Zealand still resonate in their respective countries.

"The reason they do, I think, is because they both piggybacked onto these larger social movements," Elliott says. "When Tuskegee [was revealed] it was kind of an example of what people in the civil rights movement were demonstrating against. It was the same with the women's movement in New Zealand. It became representative of a whole range of oppressive practices against women."

'Complete Silence'

In contrast, other episodes of unethical research affect a disparate and marginalized group who may have little more in common than a disease or diagnosis. Again, Elliott maintains that the New Zealand travesty has not been on the radar in the U.S., but perhaps Jones' book, *Doctors in Denial: The Forgotten Women in the 'Unfortunate Experiment,'* will change that. *IRB Advisor* interviewed Jones about his book and the legacy of the experiment.

IRB Advisor: In your book, you describe the rudimentary nature of Dr. Green's research, which lacked a protocol, a team approach, and had no clear hypothesis. Just to clarify, at the time of the study, were there no requirements for ethical review by some kind of institutional review board?

Jones: You are correct that Green's research had no "clear hypothesis," but careful reading of his words and writing does give a reasonably clear idea of his thinking. At the fateful 1966 meeting, which approved his study, the minute secretary recorded his "aim is to attempt to prove that carcinoma in situ [of the cervix] is not a premalignant disease." While institutional review boards did not exist in New Zealand in 1966, the Hospital Medical Committee acted as a de facto ethics committee. Any change in hospital policy or medical practice required approval by this committee.

IRB Advisor: You note in your book that a discussion of the Unfortunate Experiment at a medical meeting in Florida in 1978, and even your published article in 1984, failed to stop the experiment. Can you comment on this?

Jones: It caused a stir within the walls of the meeting room in Florida, but nary a ripple reached New Zealand. Despite prepublication copies of the [1984] paper being given to all members of the National Women's Hospital senior medical staff, there was not the slightest sound, whimper, or muffled comment outside the walls of the hospital following the publication of our paper. Complete silence! Seemingly everyone was paralyzed by the bad news.

IRB Advisor: That is rather extraordinary. Were the powers that be bound to a "false dogma" of sorts to protect the hospital's reputation and prevent exposure to liability?

Jones: Years before, in 1975, an in-house "whitewash" committee had examined complaints by [two faculty members] about the outcome of Green's experiment, but failed to address the central issue — patient safety. Of the 29 cases [of women with cancer] referred to the subcommittee, more than half were excluded without a reason being recorded for doing so. Of the remainder, all of whom had developed invasive cancer, the committee stated that "the staff members have acted with personal and professional integrity, but it is not within the terms of reference of the committee to comment on the outcome of the trial to which the agreed policy applies."

The committee noted that "the effect of continuation of this trial depended on the staff concerned subjugating personality differences in the interest of scientific inquiry." In essence, professional loyalties were more important to the committee than the welfare of the patients in Green's study. Liability was not an issue as New Zealand had introduced, in 1966, a no-fault Accident Compensation Act, which removed litigation except in rare circumstances.

IRB Advisor: In your opinion, could something like the Unfortunate Experiment in New Zealand occur again in another country?

Jones: My answer to this question is a qualified "yes." I do not know about the USA, but New Zealand ethics committees reach their decisions by consensus. In my story, only one man, [the late] Dr. McIndoe, argued against Green's experiment in the first instance and he was overruled by the hospital hierarchy. I do not think we can say that such an experiment could never happen again. Professional loyalties and human frailties weaken good decision-making. ■

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Clinical Trials Often Exclude Women, Even When There Could Be Compelling Benefit

New study asks women what they think

Clinical trials often exclude pregnant women, citing additional risks. However, women almost never are asked what they think about participating in those studies and the risks.

This is a mistake that some researchers are working to correct.

"Our work is part of a larger effort to make sure pregnant women's interests are represented in research, whether it involves an emergency response or not," says **Anne Lyerly**, MD, MA, professor of social medicine at the University of North Carolina (UNC) at Chapel Hill. Lyerly also is the associate director of the Center for Bioethics at UNC, and she is the principal investigator on the PHASES project, a National Institutes of Health (NIH)-funded study aimed at developing concrete ethics guidance for HIV research with pregnant women.

One part of this project is a study of how pregnant or recently pregnant women view research rules — including rules governing HIV drug clinical trials — that may exclude pregnant women.

Since the 1960s when thalidomide use in Europe led to fetal malformation — a problem the United States mostly avoided due to the FDA blocking the drug's approval — clinical trials have been hesitant to enroll pregnant women.[1]

"One thing that's been problematic is that in our ethical debates over which circumstances pregnant women should be involved in research, we have not asked pregnant women themselves about the circumstances under which they should be involved," Lyerly says.

For a long time, the IRB community has thought that its job is to protect research participants from research risks, and fetuses are included in that protection, Lyerly notes.

"The idea is that as long as you have a strict contraception requirement and protocol, and keep exposures to risks as minimal as possible and you have the right protections in place, then you are being ethical IRB members," she says. "We are challenging the ethical paradigm that it's the primary responsibility of the IRB to protect pregnant women and children from research."

This traditional view of an IRB's role does not always protect women in the end, she adds.

For instance, pregnant women who are excluded from a clinical trial might be exposed to the same or similar medication or treatment in a non-research setting, where they would not be as closely monitored.

The long-time tendency to exclude pregnant women from research might not protect them, Lyerly adds.

"If you are unwilling to include pregnant women in the research context, then they won't be well served in the clinical context," Lyerly says.

Among the different ways clinical trials handle reproductive issues, one of the most common rules is to exclude pregnant women from a study and to require all other women enrolled to use one or two forms of birth control, says **Kristen Sullivan**, PhD, MSW, MBA, PHASES project director at the UNC Center for Bioethics in the department of social medicine.

Another way is requiring paternal consent when there is the possibility of benefit to the fetus, but not to the woman who is pregnant, Sullivan says.

"Based on U.S. regulations, the study might require paternal consent when there is only a benefit

to the fetus, unless the father is unavailable or incompetent or when the pregnancy resulted from rape or incest," she says.

Another approach entails dropping enrolled women from the study drug if they become pregnant.

"If you were in a study, the benefit in the study could be to you," Sullivan says. "If you got pregnant, most studies would take you off the study and discontinue the study drug because of your pregnancy."

The research team asked 140 women, including 70 from the United States and 70 from Malawi, who were HIV positive or who were at risk of being infected with HIV and who had been pregnant within the past two years, to consider the common pregnancy and study enrollment rules. Sullivan presented the study's preliminary findings in a panel session at the PRIM&R 2017 Advancing Ethical Research Conference, held Nov. 5-8, 2017, in San Antonio.[1]

"We wanted to ask women who would be similar to populations that would either participate in HIV research or be likely to benefit from HIV research," Lyerly says. "We introduced the fact that these rules were often in place and may have applied to studies, and we wanted to know what diverse women thought about these rules and policies."

There were a divergence of views and a range of considerations that they brought to the table, Sullivan says.

More than half of the women supported the paternal consent question for a variety of reasons. Some supported paternal rights, believing the father had a shared responsibility for the well-being of the fetus, she explains.

"On the other side of the coin, many participants talked about how it was the woman who was carrying the pregnancy, and it was her body, and so it should be her choice to participate," she says. "But what was particularly interesting was the way the women explained how important it was that the relationship dynamic be considered."

Some women believed it was appropriate to include the father in these decisions, but only if he was invested and involved in the woman's pregnancy, she adds.

"SOME OF THE ISSUES THEY'VE RAISED ARE MORALLY RELEVANT, AND BIOETHICISTS AND POLICYMAKERS DIDN'T THINK OF THESE BECAUSE [WOMEN] WEREN'T ASKED."

"In Malawi, if the couple was not married, or in the U.S., if the father was not involved, many women didn't think he should have any input into the decision," Sullivan says. "The other piece had to do with women trying to avoid conflict and violence in the relationship, and for some women that was a reason to oppose paternal consent."

Those women feared that some men would not allow their partners' involvement in the study, even if the study could be beneficial.

Another challenge for clinical trial investigators is to decide how to weigh risks and benefits to the woman and fetus, and the PHASES team is working to develop an ethics framework to address that.

"There is a large and growing evidence base for treatment, using HIV medications to treat a pregnant woman to prevent disease in her newborn, and that's standard of care," Lyerly says. "Medications have side effects, and there are different levels of efficacy. More research is needed to optimize treatment regimens in pregnant women so they and their babies are best served."

This can require a trade-off, and trade-offs that involve pregnancy are ethically complicated, Lyerly says.

"What we're trying to look at, as part of our study, is how we can ensure that there is adequate evidence to make the best choices for pregnant women, in terms of their own health and in terms of preventing HIV in their children," she explains.

The study also asks women how they feel about being required to use two forms of contraception during a clinical trial.

"For example, the requirement to take birth control was viewed by some participants as problematic," Sullivan says. "They were concerned about the side effects of birth control, and they thought two forms were unnecessary, particularly for women who were not sexually active."

The study's whole point is to include women's voices in these ethical decisions, Lyerly says.

"They can offer depth and breadth to an ethical argument that's been around a long time," she explains. "Some of the issues they've raised are morally relevant, and bioethicists and policymakers didn't think of these because [women] weren't asked." ■

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How to Ensure Exempt Studies Maintain Data Confidentiality

Get IT pros involved

Whether the Common Rule changes requirements for handling exempt studies, IRBs might choose to stay involved in these decisions. How they accomplish that depends on the IRB's policies, procedures, and goals, but one important focus should be on data confidentiality.

"We have looked forward to the changes in the Common Rule, related to expanding exemptions," says **Teresa Doksum**, PhD, MPH, senior director of quality and research ethics and IRB chair at Abt Associates Inc., an independent research organization in Cambridge, MA.

"We look forward to expanding exemptions as long as limited IRB review is conducted to ensure researchers are maintaining confidentiality and have adequate provisions to do so," she says. "The way we typically handle exemption requests by a researcher is for our staff, including me and an IRB chair or administrator, to screen the project to see if it's eligible for exemption."

The same approach will apply to surveys and interviews. "If they're eligible for the new exemption category, we'll be allowed to exempt it as long as we can conduct a limited IRB review and as long as there are adequate provisions for confidentiality," Doksum says.

The IRB requires researchers to submit a minimum amount of information before it makes an exemption eligibility determination, she says.

"If they want to be exempt and they have sensitive data, we want to see what their provisions are to maintain the confidentiality," she explains. "And we have a data security plan template we use to see what their plans are to protect data."

Protecting participants' confidentiality is very important to researchers and the IRB, Doksum says.

> "WE WANT TO HELP THEM THINK ABOUT HOW TO PREPARE FOR THIS TYPE OF EXEMPTION AND TO LOOK AT PROVISIONS TO MAINTAIN CONFIDENTIALITY."

Doksum offers the following suggestions for how IRBs can make sure they maintain some control over exempt determinations:

• Read the confidentiality provisions. One way to handle the exempt status is to review all provisions for maintaining confidentiality. IRBs might still want information about projects that are exempt from IRB review so that they can ensure data security and confidentiality.

"We want to help them think about how to prepare for this type of exemption and to look at provisions to maintain confidentiality," Doksum says. "We show how we've been doing this, and it's a way to get them started to think about the main risk in the studies they do."

Some institutions have access to an IT security professional who can partner with the IRB on data security.

• Set up protocols and a data security plan. IRBs can set up protocols for data security. Although each study is different, there can be a common set of IT tools for securely transferring and storing data, Doksum says.

"The tools must comply with all federal and international standards," she adds.

Abt Associates published in 2015 a 16-page data security plan development guide for researchers. The plan includes a checklist of items each data security plan needs, including the following:

- research grant or contract;
- data use agreements;
- study design, including data collection instruments and consent language;
- protocol approved by IRB;
- Office of Management and Budget Paperwork Reduction Act clearance submission (confidentiality section);
- Privacy Act System of Record Notice;
- national and state privacy laws.

• Cross-train IRB and IT partners. "What we recommend for smaller institutions that may not have an IT expert [on staff] is they can at least cross-train," Doksum says. "Our IT security partners

and our IRB members are not researchers, so over the years we've trained them on research methods, data collection, data flow."

The IT security professionals taught IRB members enough about encryption to let them know when they really need it, she adds.

"Our advice for smaller institutions is to find a partner in their IT department and to start working together and training them and having them train you," she says.

• **Educate and monitor.** As regulations change, including changes to the Common Rule, it's important to educate researchers, IRB members, and staff on these changes.

IRBs can base education sessions on federal guidance. The same guidance could inform changes to protocols and templates.

Monitoring is part of the IRB's oversight and review process.

"After we review and approve a data security plan, our researchers check in with us to see if anything changes," Doksum says.

For example, if there's a substantive change to the study design that affects confidentiality, then researchers must come back to the IRB with updates to their data security plan, she says.

"If they add a new partner to the project or want to change the questions they're asking to include something more sensitive, then they come back to us," she adds.

The IRB also can train staff on how the exempt status is used and changed under the Common Rule.

"We're a small-volume IRB, so we have a lot of communication, every day, with researchers," Doksum says. "And they are protecting people's sensitive information because it is just as important to them as it is to us." ■

Study Looks at Use of Emergency Research Informed Consent

Two-page IC form used

Emergency research is essential to improving healthcare, but following regulatory human research protection rules can be challenging — particularly with informed consent.

Researchers studied the use of a two-page, full consent form, given by paramedics to patients who suffered a traumatic injury. Investigators conducted a randomized controlled trial that compared prehospital fentanyl/intranasal ketamine to fentanyl/placebo in patients with traumatic injuries. Paramedics provided patients informed consent before administering pain medication and transporting them to the hospital.[1]

"The study is being done in the field with EMTs, and it did not qualify for waiver or alteration of consent," says **Michael Linke**, PhD, CIP, IRB chair and volunteer associate professor of medicine at the University of Cincinnati.

"We developed a two-page consent form that contained all required elements for FDA studies and had a signature line," he says.

The IC form includes straightforward, condensed language, and doesn't require HIPAA authorization, he adds. *(See sample from two-page consent form, page 9.)*

Initially, the IRB and research team discussed wanting brief consent forms of eight pages, says **Jason McMullan**, MD, FAEMS, principal investigator of the study, ED physician, and associate professor of emergency medicine at the University of Cincinnati College of Medicine.

"We worked together as a team to make sure the document was true to the spirit of informed consent, had the required elements, and was written at a level that would be easily understandable so that we could get informed consent in this atypical environment," McMullan says.

"For this study, the primary objective is initial pain control side effects, collected directly from subjects, and so we don't have to access medical records for that," Linke adds.

Any patients that normally would receive a pain medication and who qualify for the study could be enrolled in the study and eligible for the add-on drug, says **Emily Werff**, senior regulatory coordinator at the University of Cincinnati's department of emergency medicine.

"The mechanism of injury doesn't matter," Werff says. "Some victims have had gunshot wounds; one had a broken femur."

EMTs ask patients if they're interested in the study and, if the answer is "yes," patients receive the consent form. More than 150 paramedics were trained in the consent process, the study, and human research protection, and the

training is continuing, Linke says.

"Patients have to be conscious and able to provide consent," he explains. "One potential subject was too inebriated to provide consent."

Studies of patients in pain are not new, but a study beginning outside of the hospital setting was novel and challenging, McMullan notes.

"We have five people enrolled in it, right now," he says. "One person had both arms broken and still signed the informed consent."

The medic's training was so thorough that one person caught a potential problem prior to enrolling a patient, McMullan says.

"We had one very nice case where the person met all inclusion criteria," he says. "They screened the patient and started to get consent, when the medic realized that the person had a concussion."

The medic was not convinced that the patient knew what was happening with the study, so the patient was not enrolled.

The FDA required the study to apply for an investigational new drug (IND) because the ketamine solution would be administered intranasal, and the solution was approved for intravenous and intramuscular use, but not intranasal.[1]

Researchers initially thought the study would not involve more than minimal risk or require an IND, but the IRB that reviewed the protocol disagreed. "The IRB felt it was more than likely greater than minimal risk and that it might need an IND from the FDA, so we asked Dr. McMullan to consult with the FDA," Linke says.

If the FDA had said the study was no more than minimal risk, then full consent would not be necessary, he says.

"We could have had an altered consent process with a script read to patients," Linke explains. "But the FDA reviewed it, and they felt similar to the IRB, and they required full informed consent." ■

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Sample of Two-page Informed Consent Document

The University of Cincinnati developed a two-page informed consent form that could be used in an emergency research study, involving the administration of pain medication to people who were in acute traumatic pain.

The following are a few sample items from that condensed form:

• Why is this research being performed? This research is being performed to study better ways of treating pain before getting to the hospital. The purpose of this research is to see if adding ketamine to standard pain medications improves pain control. The USAF is paying for this study.

• What is involved in the research study? You will receive a nasal spray that contains either ketamine or a salt solution. You will have a one out of two chance of receiving ketamine or the salt solution. You will be asked about your pain often, starting in about 30 minutes. You will be followed for up to 24 hours to see if you have any side effects. We may look at your medical records for information about your injury, treatment, and serious side effects.

• What are the risks of discomfort of the research study? The study drug ketamine can cause the following side effects:

- change in breathing patterns, blood pressure, or heart rate;
- nausea and/or vomiting;
- anxiousness, agitation, dizziness, dreamlike state, sleepiness, or confusion;
- double vision or involuntary eye movements;
- headache;
- producing a lot of saliva in your mouth;
- auditory and/or visual hallucinations.

There may be unknown risks to you.

As with any new medication you are given, you may be allergic to the study medication and not know it. Allergic reactions can vary from a rash to reactions as extreme as death. You will not be enrolled in the study if the paramedics are aware you have a known allergy to morphine, fentanyl, or ketamine.

• Are there benefits to taking part in the research study? You may or may not have improved treatment of your pain.

• What compensation is available in case of injury? In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. The University of Cincinnati will decide on a case-by-case basis whether to reimburse you for your out-of-pocket healthcare expenses. ■

Counterpoint: Transplant Recipients of Research Organs Entitled to Informed Consent

'Investigators are trying to turn the clock back'

Interventional research to preserve the viability of donor organs means the transplant recipient is a research subject entitled to give informed consent — period, says bioethicist **Ruth Macklin**, PhD, professor emerita at Albert Einstein College of Medicine.

Macklin refutes the contention by scholars that a concept of a blanket, "clinical consent" to receive a research organ would streamline the process. Proponents of this approach say it would remove barriers, emphasizing that "interventional research on deceased organ donors and donor organs prior to transplant holds the promise of reducing the number of patients who die waiting for an organ."[1] *(For more information, see the story in the December 2017 issue of* IRB Advisor*.)*

Macklin recently co-authored an essay[2] arguing that if the organ is manipulated in some way to prolong viability for transplant, or presumably any other reason, the recipient must give informed consent.

"Clinical consent presumes that the people who are the recipients of these organs are not research subjects," Macklin tells *IRB Advisor*. "We argue that the people who receive an organ that has been manipulated through a research protocol are research subjects. It is clear what the motivation is — as soon as you have to ask people for consent to research, there will inevitably be some people who will refuse. They may refuse irrationally, they may refuse knowingly, or refuse for no reason, but that is the right of research subjects and patients."

A high-profile case in 2015 and 2016 brought the issue into the public eye and the ethical arena. The watchdog group Public Citizen argued that kidney recipients from a hypothermia study were, in fact, research subjects and should have been asked to grant informed consent.[3,4] The Office of Research Oversight at the Department of Veterans Affairs essentially agreed with them, though the IRB in the case had ruled the study posed minimal risks to the organ recipients and that informed consent was not needed. Advocates of this type of research argue that they are trying to improve transplantation, remove barriers, and extend the viability of organs post-transplant.

> "IF THIS WERE SOMETHING UNDER THE SCRUTINY OF THE FDA — IF IT WERE AN ARTIFICIAL OR MECHANICAL KIDNEY — OF COURSE THE RECIPIENT WOULD BE A RESEARCH SUBJECT."

"My argument is basically if the organ is manipulated, informed consent is required from the recipient because the recipient is a research subject. It is no different from any other kind of research," Macklin says. "Of course, they don't want barriers, but these are the rules. This has been a standard for many, many years in treating human subjects. These investigators are trying to turn the clock back several decades and say, 'We don't really need consent for this kind of thing. Let's just call it treatment.' Well, it's not just treatment."

However well-intentioned organ investigators and their advocates are, critics like Macklin see this approach to research as a threat to a cardinal ethical principle.

"Once they start doing something to the organ, you have an organ that has been manipulated for research purposes," she says. "If this were something under the scrutiny of the FDA — if it were an artificial or mechanical kidney — of course the recipient would be a research subject. The question is, if a genuine human organ has been manipulated, why isn't that subject to the same kind of research considerations?"

Proponents of using research organs without informed consent underscore that the risk-benefit ratio clearly favors the recipient on a list awaiting a transplant. Again, Macklin begs to differ.

"The risks are whatever the standard risks to a transplant patient would be, plus the added risk of the research," she says. "When you are doing research, you don't know what all the risks are — that's why it's research. There may be great benefit to others in the future if you have these manipulated organs that turn out to be better than non-manipulated

organs, but you don't know that in advance." ■

REFERENCES

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OHRP and FDA Issue Guidance on IRB Meeting Minutes

Part of harmonization goal

The Office for Human Research Protections (OHRP) and the FDA prepared guidance to inform IRBs about how best to prepare and maintain IRB meeting minutes under both agencies' regulatory requirements.

The guidance, titled "Minutes of Institutional Review Board (IRB) Meetings: Guidance for Institutions and IRBs," was issued Sept. 26, 2017.

The joint guidance is part of the agencies' efforts to harmonize differences in human subjects protection regulations between the U.S. Department of Health and Human Services and the FDA. They are required to harmonize by the 21st Century Cures Act's Title III, section 3023. The Cures Act was signed into law on Dec. 13, 2016.

The guidance discusses examples of noncompliance as it relates to minutes, and includes these examples:

- minutes are missing;
- minutes reflect an inaccurate account of meeting attendance;
- minutes lack sufficient detail to show the vote on actions taken by the IRB, including the number of members voting and abstaining;
- minutes are incomplete and only describe voting actions as "passed unanimously;"
- minutes do not clearly indicate, or contain discrepancies about, what the IRB approved;
- minutes fail to include a summary of the discussion of controverted issues.

The guidance also discusses informed consent and how it is addressed in meeting minutes: "The minutes of IRB meetings must be sufficient in detail to show the basis for requiring changes in (to secure approval) or disapproving research (45 CFR 46.115(a)(2); 21 CFR 56.115(a)(2)). The IRB may summarize any changes to informed consent form(s) required by the IRB in the minutes, or other IRB record (e.g., an annotated informed consent form that includes IRB-required changes that gets appended to the minutes)."

The OHRP guidance can be found at: http://bit.ly/2AmXqyf. ■

IRB ADVISOR

Purdue IRB Shuts Down Youth Study

An IRB at Purdue University in West Lafayette, IN, has terminated a study of young people with high blood pressure after a youth camp last summer was plagued by multiple incidents of violence and sexual harassment.

In July 2017, the university closed Camp DASH early after a wave of incidents. The camp was part of a five-year federally funded study on the effect of salt reduction on the blood pressure of youth ages 11 to 15 years. Recurrent incidents raised concerns about the participants' safety in the camp, which was in the second year of the study. The IRB reviewed the situation to determine whether the camp should continue, and rendered the termination in a letter on Nov. 22, 2017.

The IRB ruled that the study's principle investigator, **Connie Weaver**, PhD, must submit a remediation plan and agree to additional scrutiny for future research at the university.

Weaver issued a statement in response, saying: "I am deeply saddened by the instances that caused Camp DASH to end early. As the principal investigator, I accept responsibility for events that occurred at Camp DASH. The safety and security of research participants always comes first. I have dedicated my career to nutrition science research, and our team's work has led to better health and wellness for millions of people across the world. We will continue these important efforts to find solutions to the nation's top health concerns for at-risk, diverse adolescents."

An investigation commissioned by Purdue President **Mitchell E. Daniels**, Jr., found multiple incidents of violence, bullying, inappropriate touching, and sexual harassment among study participants. These incidents were compounded by the investigators' failure to report them in a timely manner, with the suggestion in the investgation that the camp may have had insufficient staff to provide safe oversight.

In a letter announcing the decision, Daniels wrote, "Camp DASH was not a typical 'camp' of the kind held routinely on Purdue's campus. It was unique in that it was a research study, which required the adolescent subjects to be in residence and to be monitored several times daily for diet and physiological response during a total of 10 weeks."

The institutional assessment and the IRB investigation revealed "serious flaws in the study's implementation, which led to the discipline and management issues that ultimately led to its closure," Davis noted.

Similar residential research studies in the future will require the protocol to assign a qualified camp administrator to oversee "all aspects of camp operations — including screening and hiring of staff; scheduling and supervision of programs and activities; and managing living accommodations," Davis said. ■

COMING IN FUTURE MONTHS

- IRBs could start seeing studies that use tracking devices
- SBER issues with new Common Rule
- Best practices on community research training
- Best practice in handling potentially exempt studies