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HEADLINE: UC studies raise doubts about consent

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BODY:
Can delusional person recognize all the risks?

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Patricia Reynolds does not see how University Hospital can claim she was lucid enough to give her consent to an experimental drug trial. Ms. Reynolds, who suffers from manic depression, showed up at the emergency room a year agothinking she could fly and asking men to marry her.

But instead of providing standard treatment, the hospital enrolled her in a research study. It is one of several psychiatric studies that have attracted federal and state investigations of the **University of Cincinnati's** research practices.

"She was imagining herself to be an angel," said Mike Fontana, a friend who had accompanied Ms. Reynolds to the emergency room. Mr. Fontana is president of a local advocacy and education organization, the Mental Health Association. "I would hardly say she was in a state of mind where she could say, "Yes, I want to risk being in an experiment where I may not be getting any medication.' "

At stake now is whether to shut down studies, order changes in how projects are reviewed, punish individual researchers or order sanctions against the university.

In the leading investigation, by the Office for Protection from Research Risks, an arm of the National Institutes of Health, regulators have refused to discuss the research they are examining. But through interviews with mental health consumer advocates, patients, UC officials and Tristate politicians, the Enquirer has identified four studies that are drawing sharp criticism.

The four studies are a 1998 bipolar disease study that recruited patients from the emergency room to test a new medication; a schizophrenia study from the early 1980s that involved giving patients drugs to trigger manic episodes; a sensitization study from 1997 that also used drugs to trigger psychotic behavior; and a continuing study of post-traumatic stress syndrome that involves giving patients spinal taps to look for chemical signs of the syndrome.

All these studies illustrate a nationwide debate about psychiatric ethics that has

prompted hearings before the House Committee on Veterans Affairs and a National Bioethics Advisory Commission. Last week, in reaction to consumer complaints, UC officials said they will suspend one type of controversial study, called "challenge" studies.

The ethical issues include:

Recruiting people from emergency rooms who may be delusional and hallucinating, and asking them to consent to a study that may not treat their illnesses.

Failing to describe the risks in consent forms, or to ensure that people understand what they are signing.

Placebo studies, in which some patients with mental illness are given the experimental drug, while others get sugar pills that do not treat their symptoms.

"Challenge" studies, in which patients are given a chemical intended to trigger psychosis to study the biochemical roots of the condition or to test a medicine's ability to prevent or alleviate psychotic episodes.

Ms. Reynolds says her trip to the University Hospital emergency roomlast May left her so despondent that she eventually attempted suicide.

The 34-year-old Carthage resident has lived with manic depression for 20 years, so she was aware that she was having a "mixed episode," depression alternating every few minutes with mania.

At her request, Ms. Reynolds was admitted to the psychiatric ward. The next day, May 6, she realized during a conversation with a nurse that she had been enrolled in a clinical trial for a new antipsychotic, olanzapine, which is sold under the brand name Zyprexa.

"If I read (a consent form), I don't remember what I read," Ms. Reynolds said.

Ms. Reynolds recalled that the nurse said she had a 50-50 chance of receiving the new drug or being given a placebo. Ms. Reynolds said she feared what would happen if she were sent home taking nothing but a sugar pill. As she considered the danger, she became enraged and started tearing off her clothes.

According to a hospital statement, she never received the study treatment. Instead, she received standard treatment until she requested to be discharged May 7, two days after she was admitted.

Later that day, Ms. Reynolds swallowed 40 pills. She escaped death only when her mother heard her fall out of bed.

So how can a person in an agitated, psychotic state agree to be in a study?

"I think that's an extremely important question," said Dr. Randy Hillard, chairman of UC's department of psychiatry. "About 20 years ago . . . the idea was that if somebody was a psychiatric patient they had no rights or the ability to make decisions about their care. Over the last 20 years, things really changed."

Ms. Reynolds' case demonstrates how well the current system works, Dr. Hillard said.

The consent form Ms. Reynolds signed uses the word placebo repeatedly. The form includes the words "sugar pill" in parentheses.

The form also included a warning that symptoms could become worse with either olanzapine or the placebo.

Not only did Ms. Reynolds sign this consent form, but she also took a "consent form comprehension test" given by a UC staff member.

In response, Ms. Reynolds says: "They were listening to a person who claimed to be an angel."

According to UC, Ms. Reynolds was released at her request because she did not meet the criteria for involuntary commitment -- that she posed a danger to herself or others. Her suicide attempt later the same day does not invalidate the decision to release her, Dr. Hillard said.

"The law is really set up to make sure we don't get into preventive detention," he said. "Even if (the doctor) had decided to keep her in the hospital, I feel quite certain a judge would have released her."

Recruiting patients from the emergency room is important, Dr. Hillard said, because a person's physiology is different when acutely ill -- the time a study can yield the most significant results.

Second, doctors don't want to remove a person from medication when he is stable; people coming to the emergency room obviously have a problem with their current treatment.

Adil Shamoo, a professor of biochemistry at the University of Maryland and a critic of human subject research, said those reasons do not justify approaching people at their most vulnerable.

"We're talking about a high-risk experiment with no medical benefit to the individual, and the person is decision-impaired and vulnerable," Dr. Shamoo said. "We say no."

Consumer advocates question the ethics of the olanzapine study itself.

In a random, double-blind placebo study, neither the researchers nor the participants know which pill is given to whom. To researchers, such studies are the best way to evaluate a medication. The U.S. Food and Drug Administration often requires such trials to approve a new drug.

Consumer advocates allege that patients can end up worse off by participating in such studies.

Using placebos -- which requires taking people off their current medication -- can send patients into a deeper psychosis, Dr. Shamoo said. Once the study ends, the original medication may never work as well again.

To Shalmah Prince, another former UC research subject, Ms. Reynolds' recent experience is a reminder of her own 10-day ordeal during a clinical trial 16 years ago.

Ms. Prince says the effects are still with her. She was part of a "challenge" study, in which researchers induced a psychotic episode with a chemical called apomorphine to study her manic depression.

"I was never the same person again," Ms. Prince told the Boston Globe. She spoke only briefly for this story and provided some documents.

Ms. Prince went to the emergency room of University Hospital in January 1983 seeking treatment, according to legal documents resulting from a lawsuit she brought against UC. She consented to a study that required her to stop taking lithium.

The consent form did not warn about the possibility of relapse if she discontinued her medication. Without it, within days, she became "hostile, provocative," broke windows in her room and set a fire on the ward, according to legal documents.

UC legal counsel has said there were no significant undisclosed risks in Ms. Prince's case. A judge dismissed her 1995 lawsuit, saying it exceeded the statute of limitations, though he said he found the facts of the case "troubling."

Critics say challenge studies are unethical because they deliberately aggravate a health problem. They also note that, until recently, challenge studies were still going on at UC. A 1997 study to test a theory about sensitization in psychosis is one of the studies under federal investigation.

Dr. Hillard said that UC wouldn't do a study anymore like the one that affected Ms. Prince. He said the 1997 sensitization study was different in three significant ways:

Today's consent forms are far more detailed than in the 1980s. The challenge drug itself is less powerful than in the past. And the patient is without medication for a shorter period, one to three days.

On Wednesday, Dr. Hillard said his department will stop doing challenge studies until critics are satisfied.

"Nationwide, there is enough of a question about (the studies) that we will stop doing them until there is a consensus about how they should be done," he said.

The federal investigation was extended to include the Veterans Affairs Medical Center in early April, said Suzanne Tate, a spokeswoman for the center.

Dr. Tom Geracioti, head of the psychiatric department at the VA and vice chairman of psychiatry for UC, said anonymous allegations have been made about the VA experiments and the federal government is obligated to follow up on them.

"They are inflammatory and reflect a nationwide attack on psychiatric studies," Dr. Geracioti said. "We're doing very careful work, treating our patients very well. We haven't had a single complaint."

The VA has conducted a series of studies since 1993 designed to identify the brain chemicals associated with post-traumatic stress disorder to find better treatments. The studies, which are continuing, involve combat veterans as volunteers.

The investigations of psychiatric research at UC are expected to continue for weeks at least. In the meantime, some changes have begun.

In addition to suspending its challenge studies, UC has proposed creating a committee of mental health consumers, family members and researchers to review psychiatric study proposals before they go to the Institutional Review Board.

The proposal is a compromise for advocates who wanted seats on the review board itself. But Dr. Hillard predicted that the new committee process could become a national model for how universities deal with the ethics of medical research.

The controversial studies

Sources have identified four psychiatric studies at the **University of Cincinnati** and Cincinnati VA Medical Center that are being investigated

Schizophrenia study Title "Biology of Schizophrenic Subtypes -- II," conducted 1981 to 1984

Lead researcher David L. Garver, UC department of psychiatry

Purpose To define subgroups of schizophrenic-like illnesses. Potentially, the information would allow psychiatrists to predict who will respond to a given medication. This study included Shalmah Prince as a subject.

Methods Sought 35 patients a year for three years, selected from the emergency ward of the Cincinnati General Hospital (University Hospital), from other psychiatric wards and by referral.

Criticism The study deprived participants of medication without detailing the consequences, even though the research protocol states there was a "distinct possibility of spontaneous remission." Participants were recruited from the emergency room, when their ability to give informed consent could be impaired. Also, apomorphine -- a chemical that can cause psychosis -- was used to differentiate between patients.

Post-traumatic stress study

Title "Cerebrospinal Fluid and Plasma B-Endorphin in Combat Veterans with Post-Traumatic Stress Disorder," published in 1997

Lead researcher Thomas Geracioti Jr., Cincinnati VA Medical Center

Purpose To determine whether the spinal fluid of patients with Post-Traumatic Stress Disorder contains higher endorphin concentrations than normal volunteers. In theory, people with PTSD have hyperactive fear responses even in the absence of stress. Potentially, the research could lead to a test to detect PTSD or to a treatment.

Methods Spinal fluid was withdrawn via catheter over a six-hour period from 10 male combat veterans and nine "normal" male volunteers. One normal volunteer dropped out. The fluid was then tested to measure B-endorphin levels.

Criticism Lumbar puncture, commonly known as a spinal tap, is a potentially painful and risky medical procedure. Critics question the ethics of asking patients to accept the risks for a test that offers no therapeutic benefit to them, and whether low-income participants were improperly enticed by cash payments offered to all participants.

Sensitizaton study

Title "Lack of Enhanced Response to Repeated d-Amphetamine Challenge in First-Episode Psychosis Implications for a Sensitization Model of Psychosis in Humans," published in 1997

Researcher Stephen M. Strakowski, UC department of psychiatry

Purpose To determine whether patients with new-onset psychosis would be more sensitive to amphetamines than "normal" volunteers. The information could lead to new treatment for manic depression or schizophrenia.

Methods Researchers chose 13 patients with first-episode manic or schizophrenic psychosis. The four-day study included daily doses of amphetamine or a placebo. Researchers measured eye blinks, mood, level of activity, rate of speech and severity of psychosis.

Criticism Patients were psychotic, yet simultaneously presumed to be rational enough to sign a consent form. Patients who needed hospitalization were denied treatment for their illness for five days to complete the study. Researchers anticipated from the outset that the amphetamines would worsen the patients' symptoms.

Bipolar disorder study

Title "Olanzapine versus Placebo in the Treatment of Bipolar Disorder, Manic or Mixed," conducted in 1998

Lead researcher Paul Keck Jr., UC department of psychiatry

Purpose To investigate whether olanzapine, the generic name for Zyprexa, is effective in treating manic depression. This was the study that recruited Patricia Reynolds.

Methods After a week in the hospital, patients who had improved sufficiently could be released to go home, taking either the medicine or a placebo.

Criticism Researchers recruited study subjects in agitated states from the emergency room. Study participants also had a chance of receiving a placebo instead of treatment for their illness.