Human Subjects
Office of Research
UNIVERSITY OF GEORGIA

Increased Vigilance in the IRB Protocol Application Reviews

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What are the things we need to consider when reviewing an IRB protocol application?

Jesse Gelsinger Story

- Jesse Gelsinger is a kid from Tucson, AZ who has a rare metabolic disorder called Ornithine Transcarbamylase deficiency syndrome (OTCD), in which ammonia builds up to lethal levels in the blood.
- Jesse has a milder version of the deficiency and was managed until he was 17 with a low-protein diet and a regimen of nearly 50 pills a day to control his illness.
- When Jesse was 18, he was a participant in a clinical trial for a potential OTCD treatment in the University of Pennsylvania, which was a safety study aimed at moving toward a treatment for babies with OTCD, and was not intended to improve the participant's health.
- Researchers would infect the patients' liver cells with a type of cold virus, which produces enzyme that prevents ammonia buildup.

Jesse Gelsinger Story (cont.)

- Previous patients in the trial had experience flu-like symptoms, but he had a much worse reaction. Within a day:

    1. He became disoriented and showed signs of jaundice.
    2. He had an intense inflammatory response and developed a dangerous blood-clotting disorder.
    3. It was followed by kidney, liver, and lung failure.

- Four days after receiving the shot, Jesse was declared brain dead and taken off life support.

The News

"The death is the latest in a series of setbacks… that has been criticized as moving too quickly from the laboratory bench to the bedside," the Washington Post reported.

"…Even the term *gene therapy* became kind of a black label. You didn't want that in your grants. You didn't want to say, 'I'm a gene therapist' or 'I'm working on gene therapy.' It sounded terrible."

Biochemist Jennifer Doudna's interview, who later discovered the CRISPR-Cas9 gene editing.


The New York Times Magazine

The Biotech Death of Jesse Gelsinger

By Sheryl Gay Stolberg

Nov. 28, 1999

News coverage portrayed the trial researchers as overeager and under-cautious, taking shortcuts and disregarding rules meant to protect the people in their care.

What went wrong?

- Federal Health Officials discovered several troubling lapses in the conduct of the study:

1. Researchers had earlier told the FDA they would tighten up the trial's eligibility criteria, but they never followed through.
2. When 2 patients suffered serious side effects, they did not immediately inform the agency or put the study on hold as required.
3. Jesse's pretrial test showed that he had poor liver function and shouldn't have received the OTC gene injection.

What went wrong? (cont.)

5. Failures in the informed consent process.
    - Researchers hadn't told Jesse about the earlier patients' side effects or about the 2 lab monkeys killed by high doses of adenoviruses.

6. The director was accused of having financial conflict of interest having a stake in the company that owned the gene-transfer technology and would benefit if the trial succeeded.

Consequences

1. Gelsinger family sued.
   - University quickly settled for an undisclosed sum, while declining to take responsibility for Jesse's death.
2. FDA suspended the Human Subjects Research at Penn's Institute for Human Gene Therapy.
3. The director was charged with several violations and agreed to restrictions on his research involving human subjects for 5 years.
4. The university paid the federal government a $514,000 settlement.
5. The university shut the program down.

The End Result

University:

1. Strengthening the IRB that oversee its trials
2. Putting new protections for patients
3. Prohibiting researchers form having financial COI in their trials

Federal Agencies:

1. Tightened monitoring of trials
2. Increased inspections
3. Created a new system for reporting serious side effects
4. And more

Criteria for Approval
(45 CFR 46.111)

1. Risks are minimized
2. Risks/benefits ratio are reasonable
3. Equitable selection of subjects
4. Informed consent – obtained and documented
5. Data safety and monitoring
6. Privacy and confidentiality
7. Vulnerable populations – additional safeguards

Continuing Review
(45 CFR 46.109)

1. Number of subjects accrued
2. Unanticipated problems (or adverse events)
3. Withdrawal of subjects
4. Complaints about the research
5. Relevant Information – especially about risk
6. Copy of current informed consent
7. Modifications or amendments

Thank you!