When First-in-Human Studies Result in Death: Legal and Regulatory Lessons

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The Common Rule

- Applies to most federally-funded research
- Requires voluntary, informed consent so that participants can weigh for themselves the risks and benefits of contributing to human research.

- To be clear: Cannot conduct studies without consent
  - “No investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject…”

- Does not apply when:
  - Subjects cannot be identified.
  - Or to unidentifiable material
  - 45 C.F.R. § 46.116

Governmental departments codifying the Common Rule:

- Health and Human Services
- National Science Foundation
- EPA- Research and Development
- Agriculture
- Energy
- NASA
- Commerce
- NASA
- Housing and Urban Development
- DOJ- National Institute of Justice
- Defense
- Education
- Transportation
- National Institute of Standards and Technology
- Consumer Product Safety Commission
- Agency for International Development (USAID)
- Veterans Affairs - Office of Research Oversight – Office of Research and Development

via Executive Order:
- CIA
- Department of Homeland Security
- Social Security Administration
The Common Rule

- Risk to subject must be minimized
  - “…(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.” 45 C.F.R § 46.111.

- Risks must be in reasonable relationship to gains
  - “Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” 45 C.F.R. § 46.111(a)

Risks ≈ anticipated benefits + importance of knowledge gained from results

Patients or Healthy Volunteers

Therapeutic Misconception:
The unspoken hope that they will receive a positive outcome despite explicit disclaimers of benefit and clear warnings of potential side effects.

Significant Ethical Debate:

The Declaration of Helsinki

“In medical research on individual subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society”
Investigator Responsibilities for INDs

Investigator has responsibility for “ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care.” 21 C.F.R. § 312.60
Informed Consent to Human Research

For consent to be informed, researchers must explain:

- Participation is voluntary

and describe:

- Purposes, procedures, duration of research;
- Reasonably foreseeable risks or discomforts;
- Benefits;
- Advantageous alternative procedures;
- Confidentiality of records;
- Compensation or medical treatments if injury occurs;
- Where to seek answers to questions about the research and participants’s rights.
Must Disclose Alternatives

Stewart v. Cleveland Clinic Foundation (1999)

Daniel Klais
- Cancer Patient
- Enrolled in Phase III clinical trial
  - Randomized into standard treatment (Surgery and radiation)
  - Did not receive chemotherapy
  - Succumbed to cancer after 5 years

Claims
- Medical negligence in diagnosis & treatment
- Late addition
  - Defective consent claim
  - Not informed of right to be treated with chemo and radiation
  - Not informed that other hospitals could treat with both chemo and radiation
  - Never suggested he opt out

Settled quietly
Patient Ruth Corn consulted Dr. James French about a lump under her breast.

- He suspects breast cancer, and that the breast may need to be removed.
- French calls the hospital, and requests procedure and tools, at which point Corn says “If that’s my breast you are talking about, you are not going to remove it.”
- French responds “I have no intentions of removing your breast.” Same tools that he requested are used in biopsy.
- Corn signs a consent form “to James B. French, M.D., to perform an operation for mastectomy . . . upon [her], and to do whatever may be deemed necessary in his judgment.”

Corn says “she had never heard of a mastectomy and Dr. French never explained the term mastectomy.”

 Corn sues French for negligence.

- Mastectomy was “contrary to her desire and consent.”

The court grants Dr. French’s motion to dismiss.

- Corn gave consent by signing the form, “whether or not she understood the meaning of it.”

*Today, this clearly would be a breach*
Informed Consent: Breach of Duty

Must Show 5 Elements:

- Failure to disclose a specific risk.
- Materialization of that risk
- “Causation-- if the risk been disclosed, the patient, or a prudent person in the patient’s position, would not have proceeded as she did
- No exception, like an emergency, excuses the failure to disclose
- As with other claims, plaintiffs must show an injury suffered as a result
Understanding Duties in the Context of Jesse Gelsinger’s Death
The Researchers

Dr. Mark Batshaw
Principal Investigator
Today: Chief Academic Officer at Children’s National Health Center and Chair of the Department of Pediatrics at George Washington University’s medical school

Dr. Steve Raper
Principal Investigator
Today: continues in the Department of Surgery at Penn as an Associate Professor with tenure

Dr. James Wilson
Sponsor & Co-Investigator; Then, Director IHGT
Today: heads Penn’s “Gene Therapy Program,” tenured appointment in Penn’s Pathology and Laboratory Medicine department

Sources: www.childrensnational.org/research/faculty/bios/cccr/batshaw; www.med.upenn.edu/apps/faculty/index; www.med.upenn.edu/camb/faculty/gt/wilson
Jesse is patient OTC.019, 2\textsuperscript{nd} patient in this cohort. Monkeys received dosage of 1\textsuperscript{st} generation virus that is 17 fold what Jesse received of a 3\textsuperscript{rd} generation virus.
Wilson was banned from working on FDA-regulated human trials for 5 years.
Who Got Sued?

Arthur Caplan, Ph.D.
CISC Member, Bioethicist
Advisor to Researchers

Dr. Steve Raper
Principal Investigator
Today: continues in the Department of Surgery at Penn as an Associate Professor with tenure

Dr. James Wilson
Sponsor & Co-Investigator; Then, Director IHGT
Today: heads Penn’s “Gene Therapy Program,” tenured appointment in Penn’s Pathology and Laboratory Medicine department

Dr. Mark Batshaw
Principal Investigator
Today: Chief Academic Officer at CNHS and Chair of the Department of Pediatrics at George Washington University’s medical school

William Kelley, M.D.
Then Dean of Penn’s Medical School

Penn

Children’s Hospital of Philadelphia

Children’s National Medical Center (CNMC)
Who Did the Government Pursue?

CNMC agreed to pay $514,622
No admission of wrongdoing

Penn agreed to pay $517,496
No admission of wrongdoing

Dr. Mark Batshaw
Principal Investigator
Today: Chief Academic Officer at CNHS and Chair of the Department of Pediatrics at George Washington University’s medical school

Dr. James Wilson
Sponsor & Co-Investigator; Then, Director IHGT
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# Dual Lawsuits

## The Gelsingers’ Suit
- Sought Compensatory & Punitive Damages
  - For use of “unreasonably dangerous” adenovirus
- Product liability claim
- Intentional assault and battery
- Breach of duty to secure informed consent
- Intentional infliction of emotional distress
- Fraud and intentional misrepresentation
- Fraud on the FDA

## The U.S. Attorney’s Suit
- **Federal False Claims Act Violation**
- Patterned on nursing home billing fraud
- Settled before they even had a theory of the case
- Monetary settlement with employing institutions
- ‘restrictive controls on their clinical research activities,’ with the toughest controls placed on Wilson
**THE FINANCIAL DEAL**

- **Biogen**
  - Minority owner
  - Super majority control

- **Genovo**
  - COO & CEO, Marion Grossman, is former director of IHGT lab

- **Penn**
  - Penn holds 5% equity in Genovo
  - Penn wholly owns IHGT

- **Genovo gives Penn**
  - $21 Million over 5 years for Sponsored Research

- **Penn grants Genovo**
  - licenses for existing Wilson technologies and option to license new technologies

- **Wilson**
  - Holds 30% equity in Genovo
  - Director of IHGT
  - 50% of time to Research
  - 25% of time to oversee IHGT
  - 1 in 7 days for Genovo

 IHGT
1995 Regulations

- $10,000 threshold triggers disclosure requirement for SFIs Investigator deems related to PHS-funded research
- Report to PHS awarding component (NIH) must include:
  - grant/contract number
  - name of PD/PI
  - name of Investigator with FCOI
- No requirements for:
  - Public accessibility
  - FCOI training

2011 Regulations

- $5,000 threshold requires disclosure of all SFIs related to the Investigator’s institutional responsibilities
- Report to NIH must satisfy previous requirements (grant/contract number and names for PD/PI/Investigator), plus:
  - Name of entity with which Investigator has COI
  - Nature of the financial interest (e.g., equity, consulting fees)
  - Value of the financial interest
  - Institution’s basis for determination that a conflict exists
- New requirements:
  - Senior/key personnel COIs must be made publicly accessible online, or by written response within 5 business days of request
  - FCOI training required for each investigator prior to engaging in research related to PHS-funded grants

- PHS regulation 42 CFR Part 50, Subpart F and 45 CFR Part 94
Dr. Eberwine raised the issue of Dr. Wilson's involvement in the evaluation of clinical data developed from patient trials. Dr. Wilson answered that he will not be involved in the design or evaluation of the clinical trials. However, he reserved the right to be an author for any manuscripts that evolve out of any trials.

The OTCD team discussed the implications of the additional primate data on the ongoing OTCD study and concluded that these additional studies did not provide additional new information beyond what was initially submitted to the RAC and FDA and did not require immediate reporting in the context of the OTCD study.
James Wilson

- 30% ownership
- WSJ $13.5 Million in stock from buyout
- Internal Penn documents implicitly price deal at $28.5 – $33 Million

SPONSOR INFORMATION
Please be aware that the University of Pennsylvania, Dr. James M. Wilson (the Director of the Institute for Human Gene Therapy), and Genovo, Inc., (a gene therapy company in which Dr. Wilson holds an interest) have a financial interest in a successful outcome from the research involved in this study.

- “restrictive controls on their clinical research activities,” with the toughest controls placed on Wilson
- Could not sponsor a FDA-regulated clinical trial or participating in human subjects research without restriction for a five-year period
- must do retraining and education on human subjects protections, and then be supervised
- oversight by a Special Monitor of Wilson’s animal research if the findings “could influence the safety” of human trials
- Must do “lessons learned” article
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA AND
THE CHILDREN'S HOSPITAL OF PHILADELPHIA

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Children's Hospital of Philadelphia
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One Children's Center
54th Street & Civic Center Blvd
Philadelphia, Pennsylvania 19104
Telephone: (215) 390-3110

24 Hour Emergency Number
215-662-6089
(Ask for the General Surgery Resident on call)

Consent to Act as a Subject in an Investigational Study (January, 1999)
CHOP IRB #1994-7-794, Penn IRB # 366-6

TITLE
"Recombinant Adeno-virus Gene Transfer in Adults with Partial Omithine Transcarbamylase Deficiency"
Disclosure of Risk

There are three major risks that you need to consider.

(1) It is possible that the adenovirus itself can cause an inflammation of your liver. (2) It is also possible that the adenovirus may produce an immune response from your body which could damage the liver. (3) Finally, it is possible that receiving the virus now may prevent you from receiving a therapeutic dose of the virus in the future.

This is one of the first times that this modified virus has been given to people through a blood vessel. Although we believe the virus is safe, it is possible that it could cause an inflammation of the liver or hepatitis. It is even possible that this inflammation could lead to liver toxicity or failure and be life-threatening. The liver inflammation could also lead to an episode of high blood ammonia. Should this happen, treatment may require the use of phenylbutyrate, sodium benzoate/sodium phenylacetate, or even dialysis to remove ammonia. Sodium benzoate and sodium phenylacetate provide an alternate pathway or detour around the OTC block. This is the current standard for treating hyperammonemia in OTC deficiency. Side effects include nausea and vomiting. If there is liver failure, a liver transplant could be required. An immune response against the virus could cause similar problems and require the same treatment. The immune response could also mean that your body would reject this virus if it would be given to you in the future.
Disclosure of Risk

It is difficult to predict exactly how people will respond. In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis and death. To reduce this risk, we are starting at a very low dose of virus and introducing the virus into only part of the liver so that if significant damage occurs, it is likely it will only happen in one part of the liver. In the worst-case scenario, however, there is the possibility of your sustaining severe liver injury (hepatitis) requiring a liver transplantation or leading to death. It is also possible that you could develop hyperammonemia associated with the liver injury. In such circumstances medical care (including the use of intravenous sodium benzoate and sodium phenylacetate) could be necessary. The second aspect of risk to the recombinant adenovirus administration relates to your access to future therapeutic gene therapy. There is a risk that you will develop neutralizing antibodies against either the adenovirus or the OTC protein. This might reduce the possibility of your receiving this maximum dose of virus we are proposing to use is still below that which has caused any severe problems in mice or monkeys.

Source: January, 1999 OTCD Consent Form, pg 3, 7
Recombinant adenovirus administration: This study marks the first time recombinant adenoviruses have been placed in the blood stream for purposes of gene transfer. As such it is difficult to predict exactly how people will respond. There is essentially no data in humans right now with respect to possible liver injury. In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis, and death. To reduce this risk, we are starting at a very low dose of virus and introducing the virus into only part of the liver so that if significant damage occurs, it is likely it will only happen in one part of the liver. In the worst-case scenario, however, there is the possibility of your sustaining a severe liver injury (hepatitis) requiring a liver transplantation or leading to death. We think the possibility of this occurring is very unlikely. It is also unlikely but possible, that you could develop hyperammonemia associated with the liver injury. In such circumstances medical care (including the use of intravenous sodium benzoate and sodium phenylacetate) could be necessary.
Reducing the Risk

In order to decrease the risk of these problems, we will be starting out with a very low dose of the virus and will gradually increase the dose after every third patient has been tested. The dose we are starting with is only 1/20th of the dose in mice which caused no side effects. The maximum dose of virus we are proposing to use is still below that which has caused any severe problems in mice or monkeys. We are also injecting the virus into only one side of the liver so that the other side is less likely to have side effects. By measuring the function of your body organs daily, we should also be able to identify any problems early and start treatment. We also will discuss the results of testing of each group of patients within a single dose level with the Food and Drug Administration before proceeding to the next dosage group. If there are serious side effects, the study will be stopped. Serious side effects involve liver, kidney, or blood function abnormalities.

Source: January, 1999 OTCD Consent Form, pg 7
Promises of Disclosure

Any significant new findings developed during the course of the study that could affect your willingness to continue participating in the study will be provided, in writing, to you. You will be given a chance to ask questions about this new information before continuing in the study. In such circumstances, we would revise the informed consent document and offer you an opportunity to reconsider your participation.
Compliance Concerns After the Death

Questions were raised about non-compliance in a number of areas including:

- “documentation of findings,
- timeliness and accuracy of reports to the IRB and FDA including summaries of adverse events,
- completeness of protocol mandated tests,
- adherence to eligibility criteria and stopping criteria,
- adequacy of training of clinical staff,
- delivery and content of the consent process,
- completeness of monitoring of subjects following vector dosing, and
- timely notification to FDA of animal toxicity data acquired subsequent to initiation of the study.”

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

James M. Wilson *
Protocol as “living document”

The actual protocol became a living document with changes occurring in real time. The team attempted to capture these changes through four different protocol revisions, with up to 54 changes included in some of the revised protocols. The investigations revealed, however, that we did not adequately document and report all of the protocol modifications to the IRBs and to the FDA. This led to confusion amongst members of the team and misunderstandings between the FDA and the team.
More Problems

Thinly Staffed Quality Assurance

It is clear now that the Clinical and Quality Assurance (QA) groups did not have the resources necessary to assure complete compliance with all complex protocols. They were asked to cover too much territory; each clinical research nurse oversaw 12 therapy protocols at any one time, while the QA group, which numbered seven staff members at its peak, was responsible for most aspects of GMP, GCP, and GLP compliance for up to seven active INDs. Support for these programs was provided primarily from grants and contracts that, individually, did not provide sufficient Clinical and QA resources to fully support specific protocols.
Another problem that became evident during the investigation is that aspects of the protocols did not provide sufficient clarity regarding key issues such as eligibility criteria. This led to the allegation that Mr. Gelsinger was not eligible for participation in the trial based on several issues including a measurement of serum ammonia that was greater than the acceptable level of $<70 \, \mu M$. In fact, this threshold had been increased from 50 to 70 $\mu M$ in an earlier revision to the protocol. In establishing this criterion, the clinical investigators did not take into account the substantial fluctuation in plasma ammonia that characterizes this disorder, nor did they specify the specific time(s) it was necessary for the serum ammonia to be below this threshold level. Multiple serum ammonia measurements were obtained prior to and immediately after dosing Mr. Gelsinger, which fluctuated around the threshold of 70 $\mu M$. The clinicians felt this kind of fluctuation was not clinically relevant and therefore enrolled Mr. Gelsinger. However, the protocol was not written to include clinical relevance of metabolic measures in assessing inclusion criteria providing credence to the FDA's concerns.
A Thinly Staffed IRB

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<th>IRB IMPROVEMENT</th>
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The Developing Literature on Dosing

Guidance for Industry
Estimating the Maxim

July 2005
Pharmacology and Toxicology

Guidance for Industry

Questions and Answers(R2)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

January 2010
ICH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2013
ICH
“The use of individual patient pharmacokinetic and dynamic data should guide sequential dosing. A process for systematic risk assessment, like that currently used in the Netherlands, should be applied routinely to all trials with novel compounds.”
Lesson #2: If you think about reporting – then do so!

Most important thing now:
Resolve to Protect Those Who Participate in Trials at Great Risks to Themselves