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

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Federal Oversight

Recombinant DNA Advisory Committee

Institutional Oversight

Institutional Review Board

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

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

R = M x I

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

Corn v. French

(Nevada 1955)

- 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."

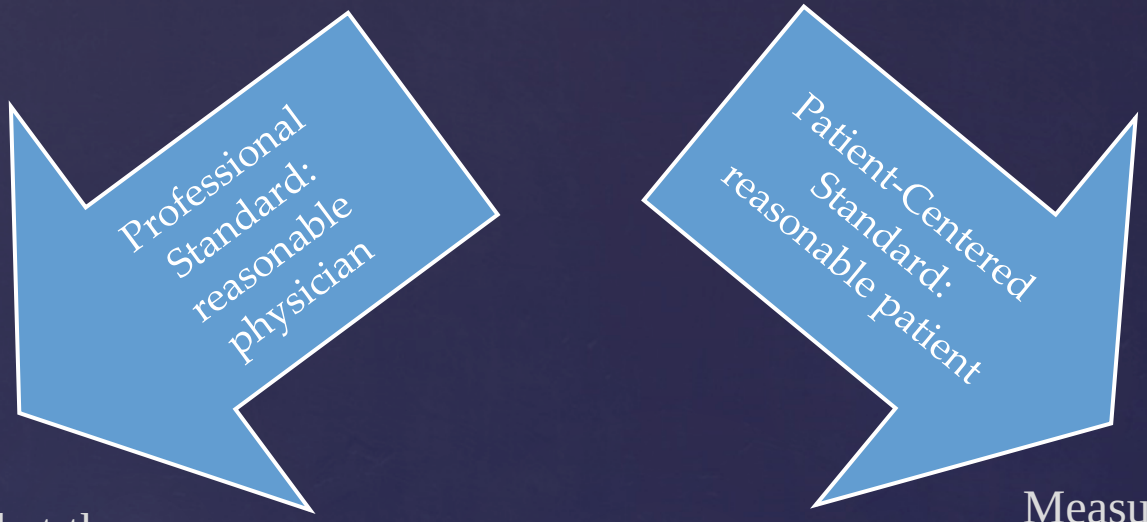
Claims at Trial

- 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



Measured by what the **reasonable physician** would disclose under similar circumstances

Measured by what the **reasonable patient** would want to know in similar circumstances

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

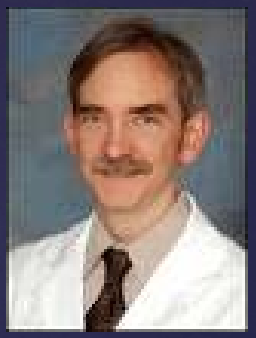
Understanding Duties in the Context of Jesse Gelsinger's Death

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

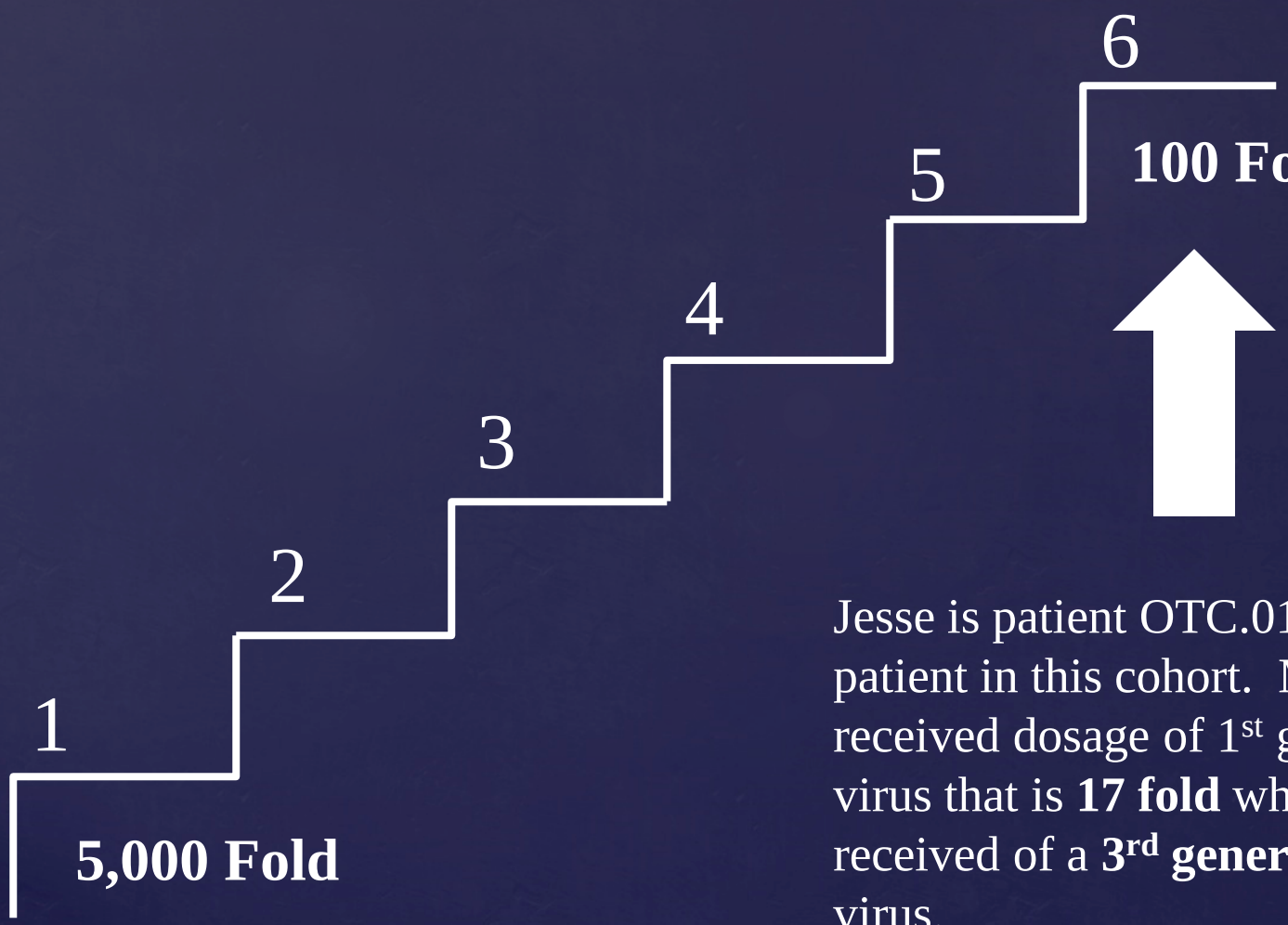
Dr. James Wilson

Sponsor & Co-Investigator; Then, Director IHGT

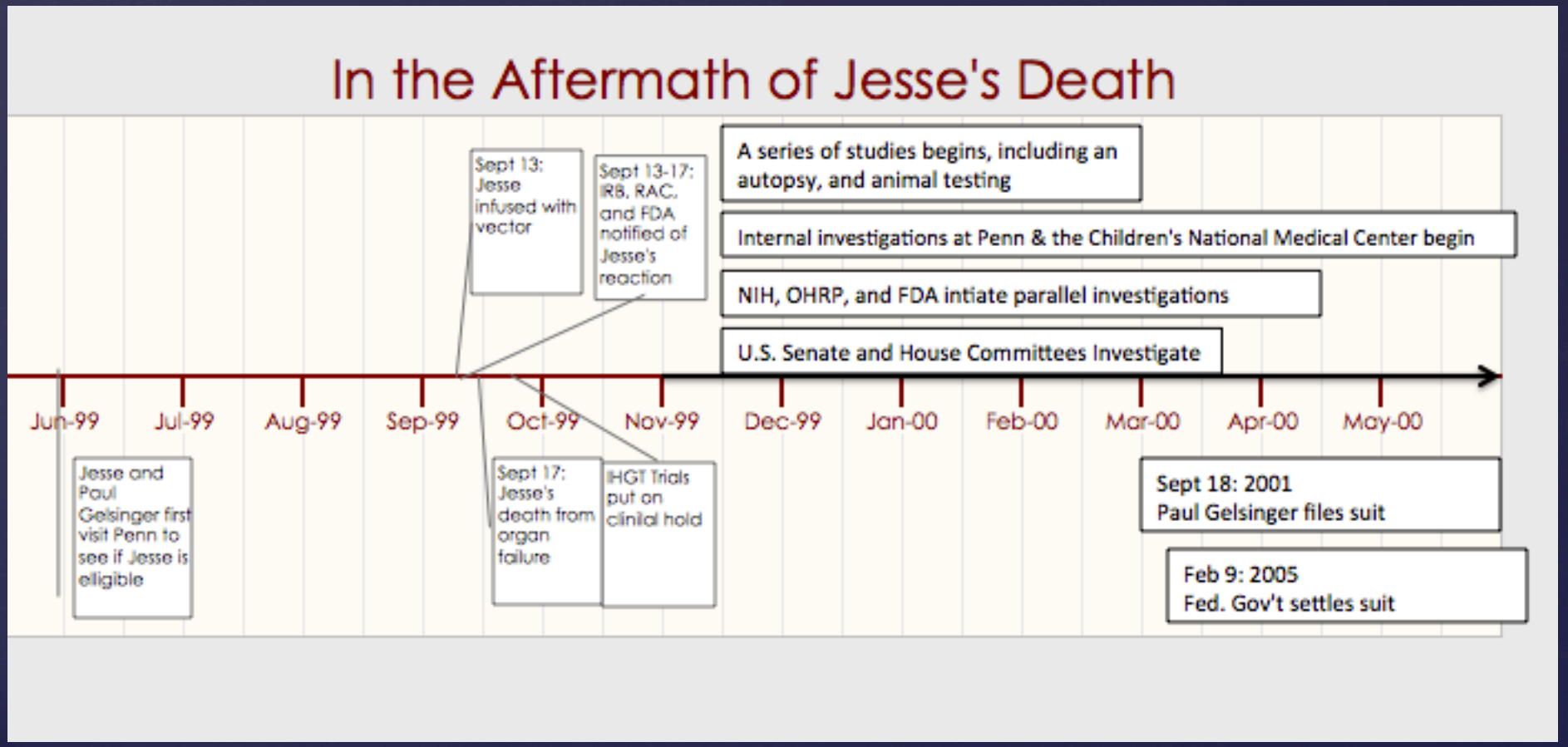
Today: heads Penn's "Gene Therapy Program," tenured appointment in Penn's Pathology and Laboratory Medicine department

Sources: www.childrensnational.org/research/faculty/bios/cccr/batshaw; www.med.upenn.edu/apps/faculty/index; www.med.upenn.edu/camb/faculty/gt/wilson

Phase1 Stair-Step Safety Trial



Jesse is patient OTC.019, 2nd patient in this cohort. Monkeys received dosage of 1st generation virus that is **17 fold** what Jesse received of a **3rd 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

Children's Hospital of Philadelphia

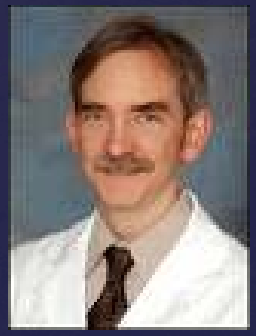
Penn

CHILDREN'S NATIONAL MEDICAL CENTER (CNMC)

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

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
Today: heads Penn's "Gene Therapy Program," tenured appointment in Penn's Pathology and Laboratory Medicine department



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

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*

Children's Hospital of Philadelphia

Penn

CHILDREN'S NATIONAL MEDICAL CENTER (CNMC)

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

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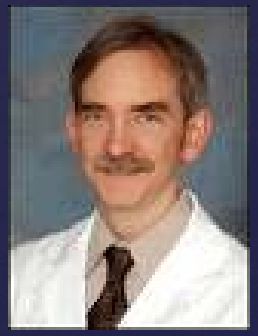

Dr. Steve Raper

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Dual Lawsuits

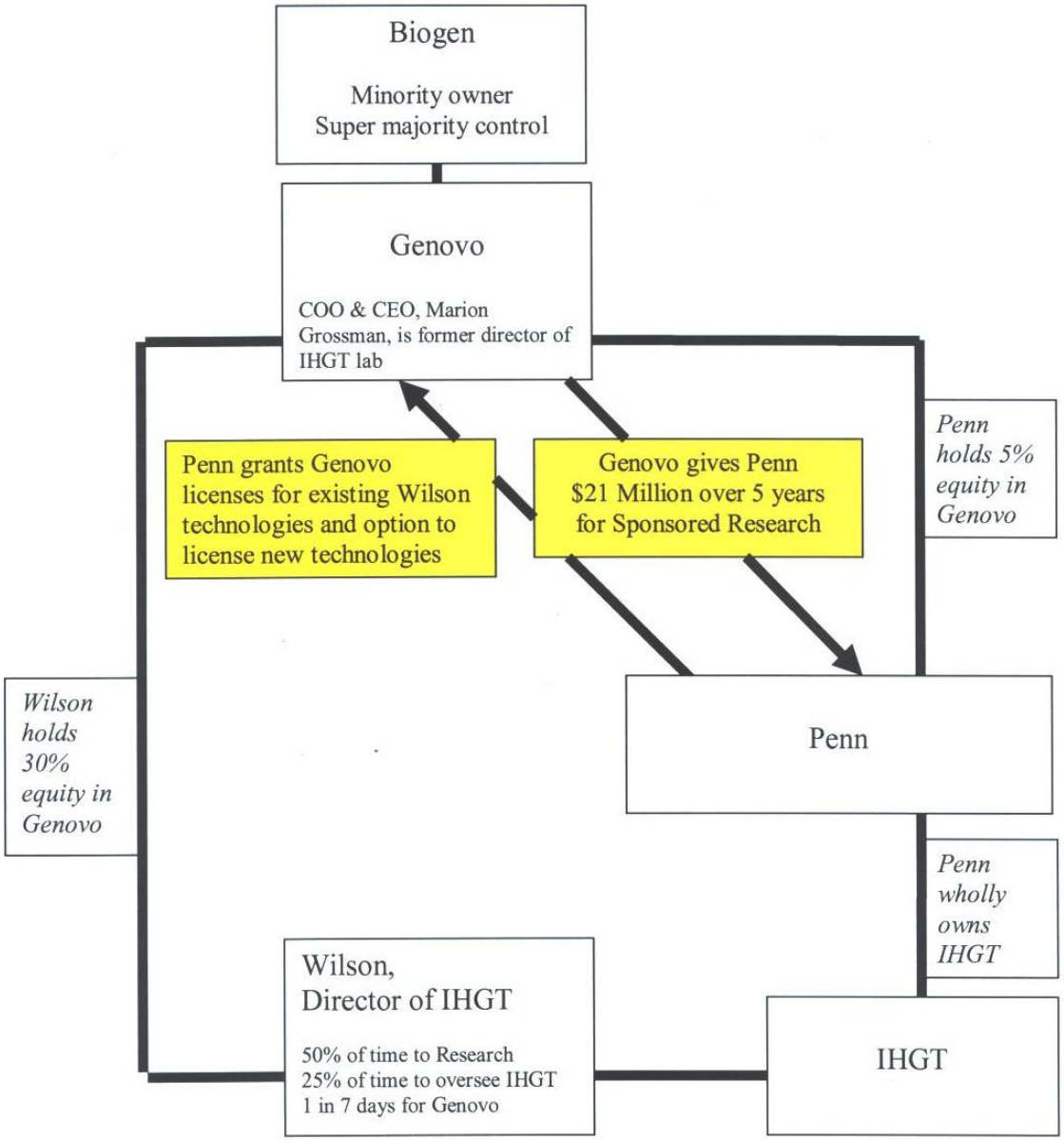
The Gelsingers' Suit

- 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



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

A Fire Wall ?

"Avoid direct participation in the conduct of clinical studies in which Genovo or Biogen ... ch studies but shall not be

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.

From discussions with CISC members and points addressed at the meeting, what follows are some of the comments and questions that were identified. The scope of the questions is in no way complete or all inclusive. At the next CISC meeting, members may conceive of additional or follow up questions to clarify any remaining concerns. T ... r significance sh

5. ... lamages if a

15. ... o assure the ... cial interests

16. Since Dr. Wilson's research efforts will be directed towards the solu ... pı ... the outcome how ... Ger

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ELSEVIER

Commentary

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

James M. Wilson *

Department of Pathology and Laboratory Medicine, University of Pennsylvania, Suite 2000 TRL, 125 S. 31st Street, Philadelphia, PA 19104-3403, USA

As described above, responsibilities for the protocol were distributed amongst three physician-scientists with complementary skills and experiences. Decisions were made in the context of "team meetings" with all constituencies present. This approach provided transparency for key decisions and invited input from all

of "team meetings" with all constituencies present. T

The OTCD team did discuss 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.

Source: CISC Draft Minutes, March 13, 1995 meeting

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

FROM [illegible]

IRB APPROVAL DATE 8/

EXPIRATION DATE 8/

HOSPIT[illegible] OF THE UNIVERSITY OF PENN[illegible]LVANIA AND
THE CHILDREN'S HOSPITAL OF PHILADELPHIA

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Co-Principal Investigator
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Children's National Medical Center
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Co-Investigators:
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Children's Hospital of Philadelphia
Outpatient General Clinical Research Center
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34th Street & Civic Center Blvd
Philadelphia, Pennsylvania 19104
Telephone: (215) 590-3110

24 Hour Emergency Number
215-662-6059
(Ask for the General Surgery Resident B on call)

Consent to Act as a Subject in an Investigational Study (January, 1999)
CHOP IRB #1994-7-794, Penn IRB # 366-0

TITLE
"Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency"

Disclosure of Risk

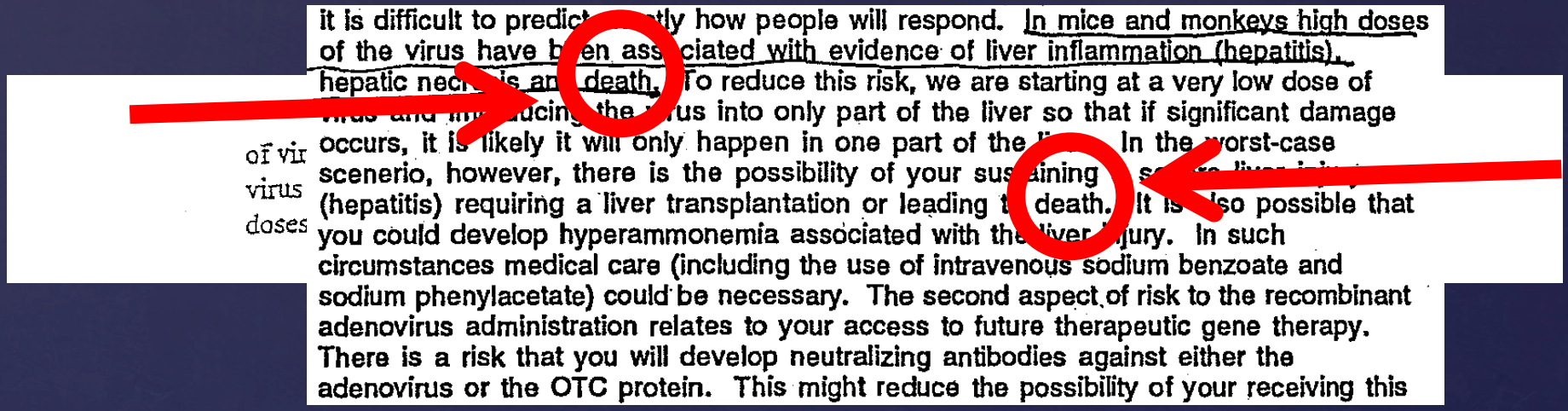
There are three major risks that you need to consider.

(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.

Source: January, 1999 OTCD Consent Form, pg 6-7

Disclosure of Risk



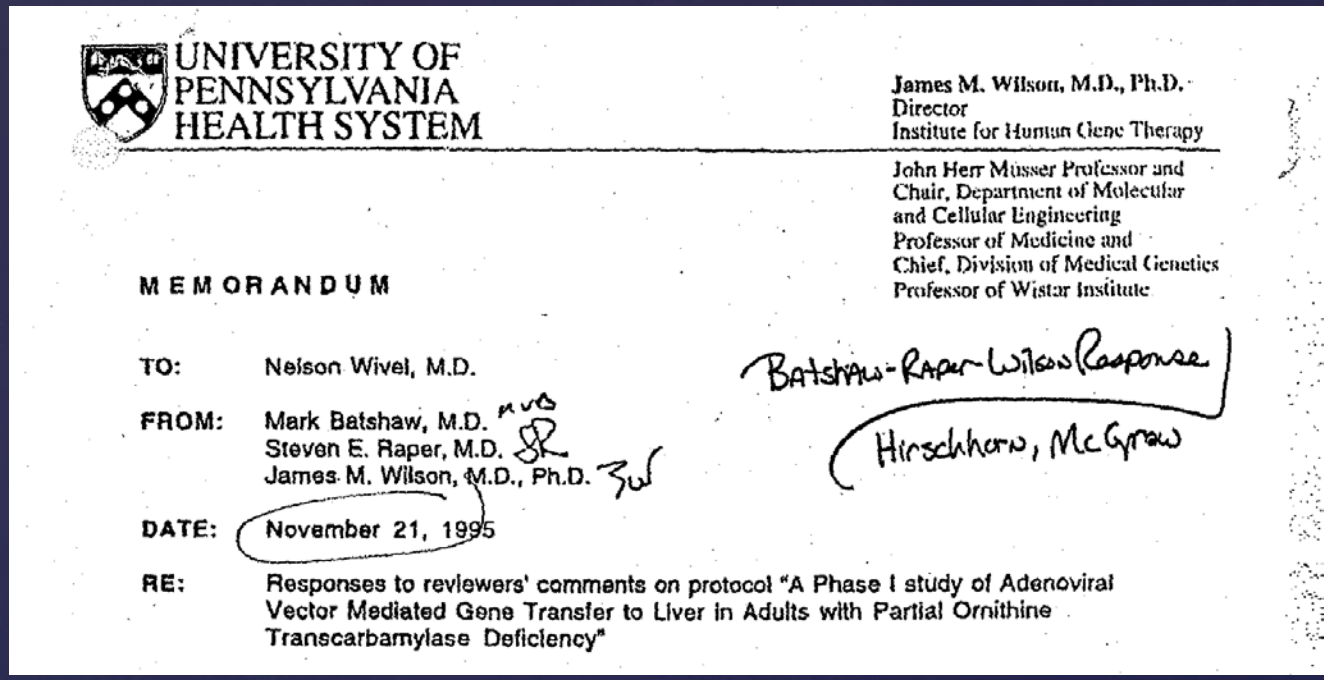
it is difficult to predict exactly how people will respond. In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis and death. To reduce this risk, we are starting at a very low dose of virus and introducing the virus into only 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 scenerio, 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

of vir
virus
doses

The 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

Disclosure Revised for RAC



UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

James M. Wilson, M.D., Ph.D.
Director
Institute for Human Gene Therapy

John Herr Musser Professor and
Chair, Department of Molecular
and Cellular Engineering
Professor of Medicine and
Chief, Division of Medical Genetics
Professor of Wistar Institute

MEMORANDUM

Batshaw-Raper-Wilson Response

Hirschhorn, McGraw

TO: Nelson Wivel, M.D.

FROM: Mark Batshaw, M.D. MLB
Steven E. Raper, M.D. SR
James M. Wilson, M.D., Ph.D. JMW

DATE: November 21, 1995

RE: Responses to reviewers' comments on protocol "A Phase I study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency"

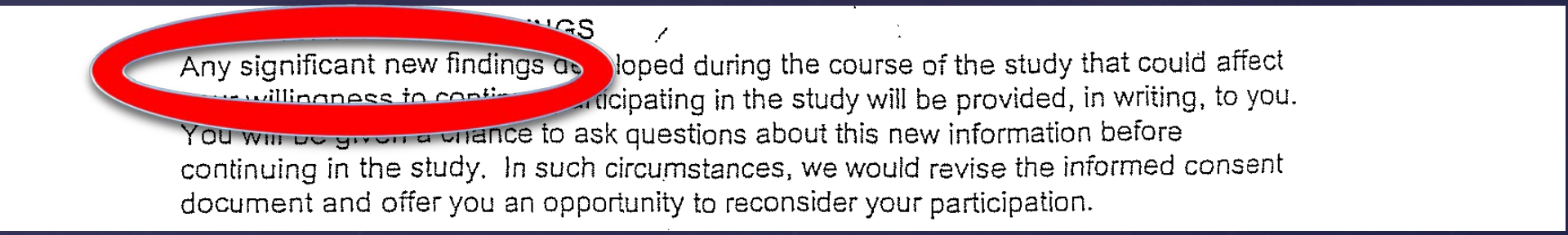
Recombinant adenovirus administration: This study marks the first time recombinant adenoviruses have been placed in the blood stream for purposes of gene transfer. As such it is difficult to predict exactly how people will respond. There is essentially no data in humans right now with respect to possible 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



...NGS

Any significant new findings de...loped during the course of the study that could affect ...willingness to conti...rticipating 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.

Source: January, 1999 OTCD Consent Form, pg 10-11

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 t[illegible] changes through four different protocol revisions, with up [illegible] 54 changes included in some of the revised protocols. The investi[illegible]tions 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.

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More Problems

Thinly Staffed Quality Assurance

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It is clear now that the Clinical and Quality Assurance (QA) groups did not have the resources necessary to assure complete [illegible] complex protocol. They were asked to cover too much territory; [illegible] clinical research nurse [illegible] therapy protocols at any one time, while the QA group, which numbered seven staff members at its peak, was responsible for [illegible] 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.

Jesse's Eligibility

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 μM. In fact, this threshold had been increased from 50 to 70 μM 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 μM. 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.

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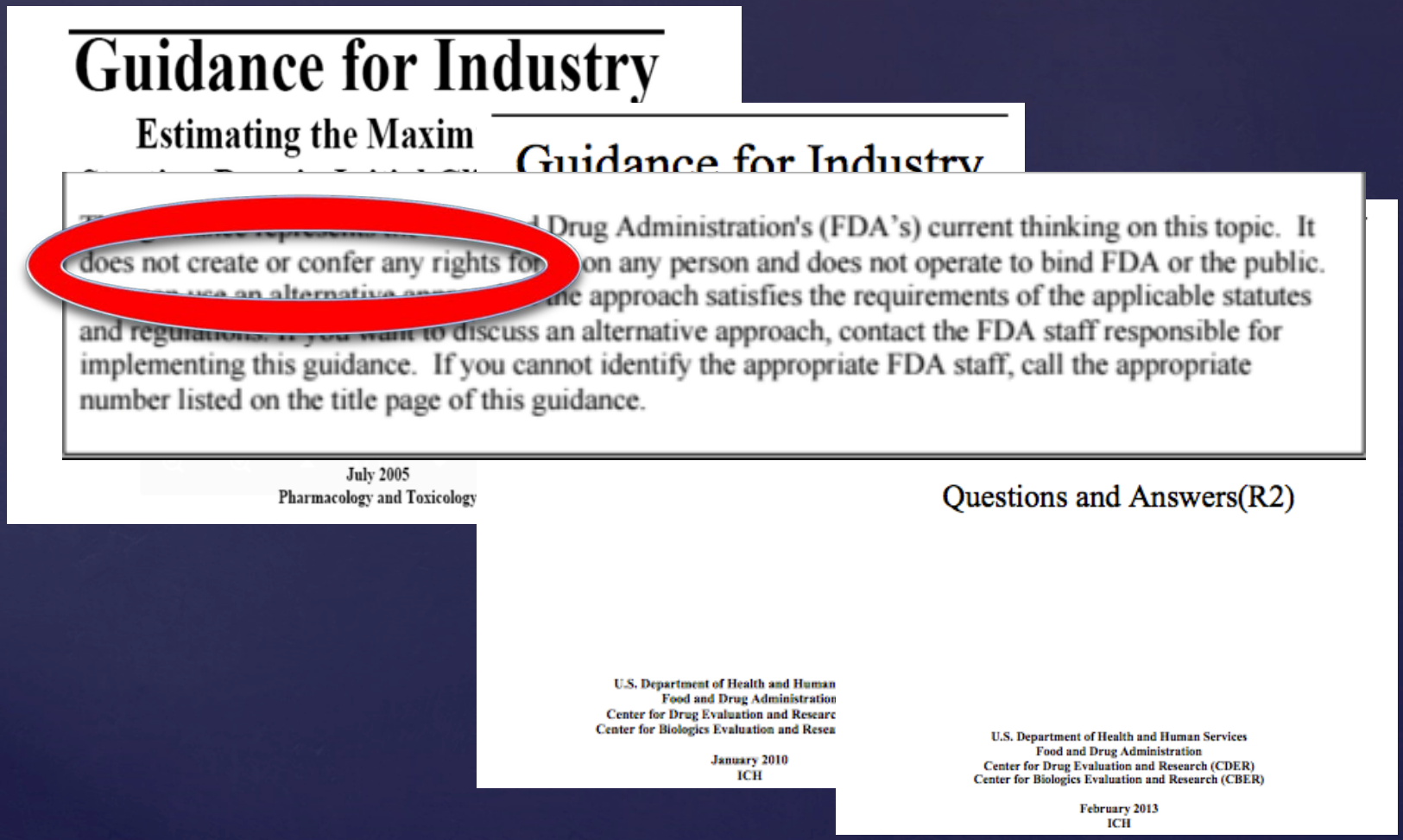
A Thinly Staffed IRB

IRB IMPROVE-MENT	**1999 (Jesse's Death)**	**2008 (*Lessons Learned)***
IRB	4	8
IRB Staff	5	23

The Developing Literature on Dosing



The Developing Literature on Dosing

"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."

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) 81 582–586 582

EDITORIAL

Implications of the BIA-102474-101 study for review of first-into-human clinical trials

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Received 22 February 2016; accepted 22 February 2016

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Over the past 10 years, thousands of first-into-human (FIH) clinical trials have been performed in Europe, with few severe adverse events (SAEs). Each has received detailed prior safety review at both the local clinical research facility and at national drug regulatory authority level. The recent fatal SAE in the BIA-102474-101 clinical trial shows the limitations of this process. Although criticized for not sequentially dosing subjects both within and between cohorts – as recommended by the European Medicines Agency for high-risk compounds after the TeGenero clinical trial disaster in 2006 – BIA-102474-101 was not considered to be high risk. Indeed, compounds with similar mechanisms of action had previously been taken through phase I and II trials without incident, and higher doses had been safely given for longer durations to nonhuman primates. If the available data are comprehensive and accurate, and further investigation does not reveal unreported warning signs, this study has serious implications for ongoing and future review of FIH clinical trials. All preclinical study documents and clinical data collected during the BIA-102474-101 trial should be made available urgently so that lessons can be learnt. In the meantime, reviewers and clinical researchers should always ask for information on drug and target interactions and full reports of preclinical toxicity studies, and plan sequential dosing with longer delays between patients and cohorts, particularly if late SAEs might be anticipated. 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.

Introduction

Drug development requires first-into-human (FIH) studies to gain initial information on tolerability, pharmacokinetics/dynamics and basic elements of drug safety [1]. All such study protocols are closely scrutinized by investigators, local review committees and the relevant national drug regulatory authority (DRA) as well as by ethics committees. The TeGenero trial, performed in the UK in 2006 [2], resulted in major changes in design [3], first in the UK, following the Duff committee report in 2006 [4], and then with revised EU guidelines in 2007 [5].

The risk assessment of FIH studies in Europe includes a review of the applicability of the preclinical toxicity studies to humans [5]. Studies that include nonhuman primates (NHPs) might be considered more applicable than those carried out in rodents and dogs, and therefore reassuring if no adverse events are noted. The risk assessment also includes consideration of whether compounds of similar structure and/or mechanism have previously been administered to humans [6]. A lack of adverse events in such clinical studies would generally be reassuring for reviewers. However, the disastrous events of the BIA-102474-101 clinical trial bring these assumptions into question.

The clinical trial

The trial aimed to take the Bial-Portela compound BIA-102474-101 (Figure 1), a fatty acid amide hydroxylase (FAAH) inhibitor, into humans for the first time. The design was a standard combination of eight single ascending dose (SAD) cohorts, food studies (pharmacokinetics with or without food) and four multiple ascending dose (MAD) cohorts receiving the compound for 10 days [7]. After receiving regulatory approval from the French DRA [Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)] and ethics approval, the first patient was dosed on 9 July 2015 [8] (see timeline, Figure 2). Forty-eight patients received single doses between 0.25 mg and 100 mg (16 received placebo) without

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Commentary

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

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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