Ethical Concerns in Gene Transfer Research

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Objectives

- **State of Gene Transfer Therapy** - The what, how and the why
- **Research Ethics** – The rules of the game
- **Ethical Considerations** – The rationale behind the rules
- **The Case of Jesse Gelsinger** – What we now know
- **Conflicts of Interest** – Identification and neutralization
- **Improving Subject Safety**
Name the Author

“To suggest that I acted or was influenced by money is really offensive to me. I don’t think about how my doing this work is going to make me rich. It’s about leadership and notoriety and accomplishment. Publishing in first rate journals. That’s what turns us on. You’ve got to be on the cutting edge and take risks if you are going to stay on top.”

Who is Liam Heffernan?
Liam Heffernan

- Two year old from Ireland
- Suffers from neurological disorder (Batten’s Disease)
  - Batten’s disease is a fatal, inherited disorder of the nervous system that begins in childhood with early symptoms appearing between the ages of 2 and 4 when a previously normal child begins to develop vision problems or seizures.
  - In some cases the early signs are subtle, taking the form of personality and behavior changes, slow learning, clumsiness, or stumbling.
  - Over time, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. Eventually, children with Batten’s disease become blind, bedridden, and demented. Batten’s disease is often fatal before children reach the double digits.

Liam Heffernan

- Batten’s disease is relatively rare, occurring in an estimated 2 to 4 of every 100,000 live births in the United States. These disorders appear to be more common in Finland, Sweden, other parts of northern Europe, and Newfoundland, Canada. Although classified as a rare disease, it often strikes more than one person in families that carry the defective genes.
- Liam’s sister died at age five from the condition in January 2011
Liam Heffernan - May 2011

- Brought to Weill Cornell Hospital, New York to undergo gene transfer therapy

Liam is fifth child to have participated in the gene transfer treatment trial which began in August 2010

Six holes drilled in skull to allow gene transfer treatment to be administered to 12 locations in the brain

Now sixteen places available each year for the surgery
Liam Heffernan - May 2011
Post-Op

- Mid-May 2011 – Patient and Pigeons doing fine

Gene Transfer Therapy

Gene Therapy Using Adenovirus Vector
What is Gene Transfer Therapy?

- Technique for correcting defective genes that are responsible for disease development

- Four approaches to Gene Therapy
  - Normal gene inserted to compensate for a nonfunctional gene.
  - Abnormal gene traded for a normal gene.
  - An abnormal gene repaired through selective reverse mutation.
  - Change the regulation of gene pairs.

Types of Gene Therapy

- Germ Line Gene Therapy
  - The introduction of genes into reproductive cells or embryos to correct inherited genetic defects that can cause disease.
  - Germline gene therapy involves altering the genetic makeup of either an egg or sperm cell before fertilization, or altering the genetic makeup of the blastomere when it is in a very early stage of division. The goal of germline gene therapy is to effect changes in the genetic code of an organism that will be passed on to future generations.
Types of Gene Therapy

- Somatic Gene Therapy
  - The introduction of genes into tissue or cells to treat a genetic related disease in an individual.
  - Somatic gene therapy involves altering the genetic makeup of the somatic (body) cells of the person undergoing the gene therapy. These cell changes are not passed on to the next generation because they are not changes to sperm or egg cells (which carry the chromosomes that are passed on), but only body cells.

Gene Transfer Research

- DNA encodes different characteristics in all living things
- All individuals, excepting identical twins, have different DNA molecules
- In some individuals, the DNA contains mutations that encode aberrant messages
- These mutations can cause abnormalities which may result in disease
### NOT Gene Transfer Research

- When DNA manipulated outside of the body but not integrated into the person’s genome – it is an example of recombinant DNA (rDNA) research.
- If protein or RNA products of the rDNA are injected into the person no gene transfer has occurred. (However, use of retroviral vectors constitutes human gene transfer.)

### Gene Transfer Research

- Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person.
- DNA may be transferred as “naked” DNA, encapsulated DNA, or DNA within another organism such as a virus.
- Use of retroviral vectors in humans also constitutes human gene transfer when the virus contains enzymes that result in a DNA copy of the RNA genome.
Goals of Research

- Human gene transfer is experimental – being studied to see if it can treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease
- Genetic errors – especially those resulting from an inborn error in a single gene – sickle cell anemia, hemophilia, cystic fibrosis
- More complex disease – cancer and heart disease
- Infectious diseases - AIDS

Research Ethics: A Brief Historical Overview

The history and development of research ethics has evolved in response to research abuses.
WW II – Nazi Doctors
Joseph Mengele

“Angel of Death”
The Nuremberg Trials

The Nuremberg Code (1947)
Nuremberg Code

- Attempt to address the atrocities of medical experiments conducted by Nazis during WWII
- Established standards required of medical research
- Recognition of an individual’s autonomy
- Requires “Informed Consent” as part of ethically acceptable medical research
- “Informed” – genuine deliberation requiring both information and understanding
- “Consent” – rational decision making requires more than just saying “yes”

Historical Cases

- **1946-1953: Fernald School**
  - Harvard, MIT and Quaker Oats.
  - Exposed young male children to tracer doses of radioactive isotopes.
  - The “Science Club.”

- **1963: Jewish Chronic Disease Hospital**
  - Chester M. Southam – injected cultured cancer cells in 22 elderly patients.
  - None told purpose of injections or that research project had nothing to do with their own health or well-being.
  - Note: three physicians (Kagan, Fersko and Leichter) resigned en banc six weeks after injection – all Jewish – Leichter a Holocaust survivor and the other two had lost family members.
Historical Cases

- **1963:** Willowbrook School
  - A New York State institution for “mentally defective” persons.
  - Dr. Saul Krugman.
  - Infected with live hepatitis.
  - Known as the “pediatric Tuskegee.”
  - Parents coerced to consent due to lack of space.

- **1966:** Beecher article NEJM
  - Article - “Ethics and Clinical Research.”
  - “Hepatitis experiments performed at the Willowbrook State School one of most serious breaches of research ethics in the post-World War II period.”

And then... Tuskegee

**The New York Times**

**Syphilis Victims in U.S. Study Went Untreated for 40 Years**

BY JEAN HELLER

The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were infected with the disease but not given treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered. The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants. Doctors in the study say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues. Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 500 black men.
The Tuskegee Syphilis Study

- 1932-1972
- Subjects: low income, African American, male with syphilis
- Informed Consent: None
- Purpose: Study the natural progression of untreated syphilis

And Still . . .

- 1999: Gelsinger – failure to disclose conflicts of interest (to be discussed in detail)
- 2000: Robertson – failure to report adverse events, inadequate informed consent
  - Dawanna Robertson – pregnant – experimental melanoma vaccine.
  - Enrolled subjects who did not meet criteria.
  - Failed to inform of relevant risks.
  - Misrepresented information to obtain governmental permission.
And Still . . .

- **2001: Roche – failure to discover serious risks**
  - Ellen Roche, 24 year-old volunteer, died while participating in an NIH-funded study at the John Hopkins School of Medicine to understand physiological mechanism of asthma.
  - IRB approved research requiring inhalation of unapproved drug hexamethonium.
  - Failed to discover older published studies reporting serious side effects.
- **2001: Grimes – risk/benefit, informed consent**
  - Lead abatement study.

Why do the Abuses Continue?

- **Changing nature of research**
  - From lone scientist to multicenter trials.
  - Corporate sponsorship of research.
  - $$$
- **Increased workload**
  - 40 protocols to 300/yr.
  - In 1974, Duke University reviewed 400 protocols, by 2001 they reviewed 2200 annually.
Treatment v. Research

- Treatment:
  - “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose ... Is to provide diagnosis, preventive treatment, or therapy to particular individuals.”

  *Belmont Report* (emphasis added)

A Definition of Research

- “a systematic investigation including research development, testing, and evaluation; designed to develop or contribute to generalizable knowledge.”

  *45 CFR 46.102 (d)* (emphasis added)
Key Ethical Considerations

- Beneficence
- Respect for Persons
- Justice

Respect for Persons

1. Individuals should be treated as autonomous agents; and
2. Persons with diminished capacity are entitled to protection.
   - This is embodied in Informed consent
Autonomy

- Means that you can rule yourself. Concept of permission
- Implies a respect for others
- We have a duty to treat, but not to judge

Benificence

1. Do not harm; and
2. Maximize possible benefits and minimize possible harms.
Justice

1. Who will receive the benefits of the research?
2. Who will bear the burdens of the research?

Applying the 3 Principles

The principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

Belmont Report
Informed Consent

Overview

“Informed consent is based on respect for the individual and, in particular for each individual’s capacity and right both to define his or her own goals and to make choices designed to achieve those goals.” (President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research)

• Thus, consent is, and must be, part of the research design
Overview

- Several sources exist which provide guidance and enumerate requirements for informed consent.
  - The Belmont Report
  - State Law
  - The Common Rule

Sources of Guidance: The Belmont Report

- Voluntariness
- Information
- Comprehension

These principles are memorialized – codified at 45 CFR 46 (The Common Rule).
Sources of Guidance: State Law

- Another source of authority for informed consent may be state law.
  - E.g. California Health & Safety Code § 24173 lists 11 elements that might influence one’s decision to participate in research including:
    - “The name of the sponsor or funding source . . . Under whose general aegis the experiment is being conducted.”
    - “The material financial stake or interest, if any, that the investigator or research institution has in the outcome of the medical experiment.”

Sources of Guidance: The Common Rule

- The Common Rule – 45 C.F.R. 46
  - Applies to research involving human subjects
  - 6 categories of research are exempt including:
    - “Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”
Sources of Guidance: The Common Rule

- 45 C.F.R. 46.116 requires 8 specific elements of informed consent including:
  - Statement of risks, benefits and alternatives
  - Statement describing methods for maintaining confidentiality, and
  - Statement that participation is voluntary and that subjects are free to withdraw at any time

Sources of Guidance: The Common Rule

- Other elements may also be necessary including:
  “A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”
Consent Waiver—45 C.F.R. 116 (d)

1. The research involves no more than minimal risk to the subjects.
2. The rights and welfare of the subjects will not be adversely affected.
3. The research cannot practicably be carried out without the waiver.
4. When appropriate, subjects will be provided with pertinent information after participation.

In order to do this, these 4 requirements must be met and documented by the IRB.

Free and Informed Consent

For consent to be morally and legally meaningful, individuals must be:

- Able to understand what they are told about their condition and capable of exercising judgment.
  - Competence/Capacity
- Be provided with relevant information about their illness and the proposed treatment for it in an understandable form.
  - (T.A.R.P.)
- Free to make a decision about their treatment without coercion.
Conclusion

• Informed consent is essential for respecting the autonomy of participants

• Informed consent is an ongoing process, not a document.

Jesse Gelsinger

• In 1999 Jesse Gelsinger becomes the first person to die in a gene therapy trial.
Ornithine Transcarbamylase Deficiency

- Ornithine Transcarbamylase Deficiency (OTD) is a recessive X-linked genetic defect which interferes with the metabolism of ammonia by the liver
- Affects 1 in 40,000 to 1 in 80,000 people
- It is a single gene enzyme deficiency
- Excessive levels of ammonium ion in brain can lead to life-threatening encephalopathy, coma and brain damage.
- Complete deficiency – death at infancy
- Partial deficiency – can be handled with a low protein diet supplemented with oral medication

Dr. James M. Wilson

- Recruited by University of Pennsylvania from University of Michigan
- Leading gene transfer researcher in the world
- Director of Institute for Human Gene Therapy and professor and chair of Department of Molecular and Cellular Engineering at the School of Medicine
- In 1992 while at Michigan Wilson founded Genovo, Inc. which had the right to market his discoveries relating to gene transfer
- Held patents relating to using vectors derived from the adenovirus
Genovo, Inc.

- In 1999 Genovo provided more than $4 million a year to the Institute, substantial portion of its budget
- Wilson and family had 30% non-voting interest in Genovo
- Penn had a 3.2% equity stake in Genovo
- Penn Conflict of Interest Standing Committee – didn’t end Wilson’s financial arrangement; rather, sought to manage it by reducing his managerial and scientific control

The Research Study

- Between 1997 and 1999 – 18 subjects participated in clinical protocol
- Wilson was co-investigator and sponsor
- Steven E. Raper, surgeon at Penn
- Mark L. Batshaw – Children’s Nationals Medicinal Center in Washington, D.C.
- Purpose was to “establish a safe dose of recombinant adenovirus to serve as a treatment for adults with partial OTC deficiency”
- Phase 1 study of escalating doses of the vector
The Research Study

- Reviewed and approved by the RAC, FDA and human subjects review boards of University of Pennsylvania Medicinal Center and Children’s Hospital of Philadelphia
- NIH and Genovo were the major funders of the research and of Wilson’s laboratory

Informed Consent Document

The informed consent document cited three major risks:

1. The possibility that the adenovirus would inflame the liver. “It is even possible that this inflammation could lead to liver toxicity or failure and be life-threatening.”

2. The possibility that the adenovirus would provoke an immune response that would damage the liver.

3. The possibility that receiving the vector would prevent the research participant from receiving it as a part of a therapy in the future.
Informed Consent Document

- Informed consent document contained a one sentence statement about the financial interests of the sponsors: “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.”

The Research Study

- Known controversial aspects
  - Study would enroll adults with mild disease; rather than children with severe disease.
  - This made informed consent easier.
  - More difficult to recognize life-threatening event in children who were already dying.
Jesse’s Participation

- Jesse suffered from a partial OTC deficiency
- He had a unique mutation – mosaicism
- His disease was controlled through diet. (Batshaw)
- He was 18 and youngest subject in study
- On Monday, September 13 1999, Jesse was injected with adenoviruses carrying a corrected gene in the hope that it would manufacture the needed enzyme
- 18 hours after infusion he developed altered mental status and jaundice – experienced by no other participant
- This lead to multiple organ system failure and acute respiratory distress
Jesse’s Participation

- Jesse died on Friday, September 17th at 2:30 PM., 98 hours following gene transfer
- After Jesse’s death the study was halted

The Aftermath

- The FDA, NIH and the Office for Protection from Research Risks at the NIH began intensive reviews of the protocol
- The found various deficiencies:
  - Jesse should not have been allowed in the trial because his liver was not functioning at the required minimal level.
  - The failure to immediately notify the FDA when earlier participants had “Grade III” liver toxicity.
  - FDA was not promptly informed about results of tests in laboratory animals that suggested a significant risk of the adenoviral vector for human subjects. At higher dosages some rhesus monkeys had died.
The Aftermath

- The researchers had changed the protocol multiple times without notifying the FDA and failed to make the changes that they had agreed to make (including tightening the inclusion criteria).
- Questioned Wilson’s and Penn’s financial interests.
- Deficiencies in the informed consent process.
- Downplaying the risk by failing to give potential participants all relevant safety data.

The Gelsinger Suit

- For several months after his son’s death Paul Gelsinger supported his son’s doctors.
- At meeting of RAC he received all relevant data relating to his son’s death.
- In September 2000 Jesse’s family filed a civil suit against the lead researcher, the University of Pennsylvania and others.
- In November 2000 the suit was settled out of court without admission of liability or disclosure of details.
The Federal Government

• FDA began proceedings to disqualify Wilson from performing clinical research with investigational drugs citing six violations:
  1. failure to fulfill the general responsibilities of investigators
  2. failure to insure that an investigation was conducted according to the investigational plan
  3. failure to submit accurate reports about the safety of the study to the University of Pennsylvania IRB
  4. failure to accurately and completely identify changes in the research for review and evaluation by the review board
  5. failure to properly obtain informed consent
  6. failure to maintain accurate case histories of the research subjects
Financial Conflict of Interest

- Private Industry provides about $1.5 billion to academic research each year
- Researchers in a trial or study often stand to make small to significant financial gains from research
- Federal Agencies and IRB’s now require investigators to disclose financial interests in trials

Wilson’s Financial Conflict

- This is the most famous conflict of interest case in medicine and we have known almost nothing about the true stakes for almost a decade
- Wall Street Journal estimated at $13.5 million
- Internal Penn. documents show Wilson’s stake in Genovo at between $28.5 and $33 million
Resolution

- Charges brought under Federal False Claims Act
- Settlement reached in February 2005
- Penn paid a fine of $517,496 and agreed to increase IRB oversight of clinical research
- Children’s National Medical Center agreed to pay $514,622 and to increase its IRB budget and staff

Resolution

- Wilson agreed:
  - Not to serve as a sponsor of a clinical trial regulated by the FDA or to participate without restriction in research involving humans until February 2010.
  - To meet specified educational, training, and monitoring requirements related to his research and to lecture and write an article on the lessons of human research participants protections learned from the OTC deficiency trial.
Name the Author

“To suggest that I acted or was influenced by money is really offensive to me. I don’t think about how my doing this work is going to make me rich. It’s about leadership and notoriety and accomplishment. Publishing in first rate journals. That’s what turns us on. You’ve got to be on the cutting edge and take risks if you are going to stay on top.”

- Dr. James M. Wilson

A Case of Firsts

- Families Suit
  - Jesse first person to die in a human gene-therapy trial.
  - Family’s lawsuit first high profile case based upon these claims.
  - First to name a bioethicist, Arthur Caplan, as a defendant.
  - First to highlight financial conflicts of interest.

- Government Suit
  - First suit of this type under Federal False Claims Act.
  - Bar researchers.
  - Wilson monitored for a decade.
Wilson’s Lessons Learned

- Wilson’s “Lessons Learned” article - published 2009 in *Molecular Genetics and Metabolism*
  - The clinical protocol is a contract with the research subjects and regulatory agencies that must be strictly and literally adhered to.
  - If you think about reporting – then do so.
  - It is very difficult to manage real or perceived financial conflicts of interests in clinical trials.
  - Informed consent may require objective third party participation.

Debate Regarding Financial Conflicts

- Pro-industry funding position:
- American Council on Science and Health (ACSH) stated in 2008:
  - that it sees “very real harm that can result from limiting industry/university collaborations.”
  - that “the collaboration between science and industry has been threatened by the development of a movement that proposes to end or drastically limit such cooperation on the grounds that it involves unacceptable conflicts of interest.”
Debate Regarding Financial Conflicts

- Ban goes too far “because two mechanisms currently in place to protect the integrity of scientific research,” peer review and disclosure suffice to prevent abuse.
- The ACSH claims that disclosure rules are better than “prohibiting those with potential conflicts of interest from engaging in certain types of professional activity.”
- But would this have worked in Jesse’s case - see Wilson’s statement. Also, how much disclosure.
- Was Wilson’s stake necessary to obtain the sponsored research agreement.

Debate Regarding Financial Conflicts

- Institute of Medicine (IOM) in 2009 would presumptively bar nearly all equity stakes by researchers like Wilson (dominant view)
  - “individuals generally [should] not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research.”
  - Goal is to “prevent undue influence or erosion of confidence in the research enterprise.”
  - Would make an exception if the “research could not be conducted effectively or safely without the individual’s participation.” Then role limited to consultant and not investigator with no role in recruitment, enrollment or informed consent.
Does a Middle Ground Exist?

- Professor Robin Fretwell Wilson proposes that the way forward is through aggressive monitoring.
- Post-approval monitoring as with IRB process.
- Goals are to: ensure the rights and well-being of research subjects,” as well as “ensur[ing] compliance with federal, state, local and institutional . . . Guidelines.”
- Suggest marrying “the IRB and conflict of interest approval processes with medicine’s invigorated culture of regulatory compliance.”

Does a Middle Ground Exist?

- In theory all human trial are subject to ongoing review by the IRB. However, in practice, the trials watched most closely in the post-approval process are those that moderate to high risk to subjects. Investigator-initiated studies, and, most relevant, studies with possible conflicts of interests
- Do away with randomness and create mandatory triggers
- To avoid over-inclusion monitoring threshold should be determined by the institution
Does a Middle Ground Exist?

- Will create substantial additional cost
- Could be treated as a "loading charge"
- Also a matter of perspective – Penn.’s SRA with Genovo called for $21 million for research over 5 years. If $100,000 was allocated to monitoring this would be less than one-half of one percent of the sums received by Penn.
- Savings = costs of suit, fines, loss of funding, reputational damage

IRB’s

- Responsible for the protection of human subjects
- Charge at 45 CFR 46
  - Beneficence: ensure the risks don’t outweigh the benefits.
  - Autonomy: informed consent process & form.
  - Justice: Benefits and burdens dispersed evenly.
- Multidisciplinary membership
IRB’s are authorized to:

- Approve, modify, disapprove research
- Observe research & consent process
- Obtain verification that no change in research
- Suspend or terminate research for noncompliance or serious harm

Private IRB’s

- Case of Jolee Mohr – rheumatoid arthritis trial
- Seattle based Targeted Genetics
- IRB Western Institutional review Board – 1981 – 16 new applications; currently 2,000-2,500 new applications each year
- IRB was a “for-profit enterprise also on Targeted Genetics’ payroll.” *Seattle Post Intelligencer*
- Line is blurred when “traditional” IRB’s charge investigators for services
Research Subject Advocate

- Tomas Jose Silber
- Thesis – “Adding research subject advocates to the genetic transfer research enterprise may add a significant level of protection for research participants.”
- RSA’s job is to be an ombudsman for research participants
- Not “ethics police” or “enemies of research”

Research Subject Advocate

- Three levels of intervention
  - First – grounded on ethical integrity of the individual researcher (i.e., adheres to the principles of the Belmont Report).
  - Second – the IRB’s ethics review and concern with compliance.
  - Third – assuring that every participant engages in voluntary, autonomous decision-making, is centered in the process of obtaining informed consent.
  - Fourth – created by addition of RSA. “allows a skillful advocate of research for research participants, who is independent from the research team, paid from a different source, and responsible/reporting to the head of the institution.
The Patient’s Perspective

- Suzanne Pattee
- Include more research participants as partners in the development of clinical trials and informed consent materials
- Educate participants about the risks inherent in phase I gene therapy trials and consulted on the development of informed consent forms

The Patient’s Perspective

- Suggestions:
  - Provide greater public education about clinical trials to address concerns raised by cases such as Gelsinger and Mohr.
  - Include people who have participated in clinical trials as partners in developing trials and informed consent materials.
  - Establish centralized IRB’s and include disease specific experts.
  - Encourage more use of central data and safety monitoring boards (DSMB) for all phase I trials.
Responsibilities of Researchers

“The extraordinary promise of science and technology carries with it extraordinary responsibilities. It is incumbent upon both scientists and public servants to ensure that science serves humanity always, and never the other way around.”

Clinton, 279 Science 1111 (1998)

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Resources


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