

Research Ethics and Conflicts of Interest in Clinical Trials

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Conflicts of interest

- Area of great current concern
- Highlighted in some recent cases where human subjects were not protected adequately
- Rules and regulations are still evolving, at both national and institutional levels
- Complex and difficult problem

It is important to manage conflicts of interest in all areas of research

- Research using human subjects deserves special scrutiny
- Interface with medical care raises special issues and concerns (e.g. privacy)
- The stakes are higher
 - The welfare of human subjects is at stake
 - Especially problematic when subjects are facing a potentially deadly disease like cancer
- The rules are often different, tougher

Why did this subject suddenly spring into the headlines?

On September 17, 1999 Jesse Gelsinger, an 18 year old volunteer died in a Phase 1 “gene therapy” trial performed by the Gene Therapy Institute of the University of Pennsylvania.

The OTC Trial

- The trial was an attempt to correct an inherited deficiency in Ornithine transcarbamylase (OTC), a liver enzyme that removes ammonia from the blood.
- An attenuated adenovirus vector containing the gene for OTC was infused into a blood vessel feeding the liver.
- In theory, the vector would be taken up selectively by the liver cells and the liver cells would then begin to make OTC, correcting the metabolic problem.
- Jesse Gelsinger was the 18th subject enrolled in this dose-escalation trial. He received the highest dose of the OTC vector ever given to a person.

The problem

- The virus invaded not only the liver, but also many other tissues.
- This activated the immune system and lead rapidly to a systemic inflammatory response.
- Within hours, Jesse's temperature was 104.5°.
- The next day Jesse went into a coma.
- His kidneys, lungs, and other organs began failing
- Despite intensive medical support and interventions he soon died.

As the investigation of Jesse Gelsinger's death by the University, the FDA, the NIH, other oversight organizations and the press proceeded, a variety of very disturbing facts and issues came to light.

Issues related to the design of the trial

- Decision to infuse the vector into the liver
- Decision to use relatively healthy adult patients, rather than babies in initial crisis
 - This change from the initial proposal to treat babies in crisis (half of whom would die of their disease) to adults with relatively well controlled disease (who were at less risk of death from their disease) was made on advice of a bioethicist
 - This change was not sent to some of the agencies that should have reviewed and approved the final protocol

Issues related to the conduct of the trial

- Jesse Gelsinger did not meet the inclusion criteria for the trial (his ammonia levels were too high).
- Two monkeys in preclinical studies had died with symptoms suggesting the same syndrome
- Two previous subjects, who received lower doses of vector, had symptoms of the same generalized infection and immune response. According to the protocol, the trial should have been halted after these adverse events, before Jesse was entered.
- Eligibility forms for patients were not filled out before entry, for any of the 18 patients. The forms were filled out after Jesse's death.

Issues related to consent

- Information on primate deaths had been removed from the consent form given to the subjects.
- The previous adverse events were not mentioned on the consent form given to the Gelsingers.
- Websites used to recruit subjects presented overly optimistic information on the trial and potential benefits.
- Changes were made in consent forms after approval by the IRB and oversight agencies, without re-review or re-approval.
- Consent was not adequately documented for 9 patients.
- Information on conflicts of interest of the researchers were not disclosed on consent forms or discussed with the subjects.

Issues related to conflicts of interest

- The PI held patents on several gene therapy delivery techniques, with the potential for large profits.
- PI founded and held very significant equity in the biotech company that would benefit if this trial were successful.
- The University also had very significant equity in the company.
- The Gene Therapy Institute received large amounts of money from the company for research.
- The reporting structure of the Gene Therapy Institute was flawed. The PI headed the Institute. The investigators and the IRB reported to him.

Some results of this tragedy

- FDA halted all gene therapy trials at Penn and reviewed gene therapy trials everywhere
- Penn barred the Gene Therapy Institute from performing any clinical trials
- RAC, NIH, and FDA reviewed rules, procedures, and records on all gene therapy trials in US
- FDA disqualified the PI; other investigators received warning letters
- The PI resigned as head of the GTI
- There were Senate hearings
- Jesse Gelsinger's family sued the PI, the research team, the University, Children's Hospital of Philadelphia, and the ethicist. The defendants settled in 6 weeks.
- New regulations and new rules for clinical research
- New emphasis on conflict of interest and its effects

What is conflict of interest?

The term "conflict of interest" in science refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research. The bias such conflicts may conceivably impart not only affects collection, analysis and interpretation of data, but also the hiring of staff, procurement of materials, sharing of results, choice of protocol, and the use of statistical methods. Conflicts of interest can affect other scholarly duties as well, but are particularly important to consider in biomedical and behavioral research because of the impact such conflicts can have on human health.

AAMC guidelines

Important elements in AAMC description

- Effect of COI on professional judgment as the critical factor
- Financial and non-financial conflicts
- Impacts of COI can permeate the entire research process – from design to reporting
- Effects of COI go beyond research
- Conflicts of interest can never be eliminated
- Appearance of a COI can be as important and damaging as an actual COI

Apparent conflicts of interest

The mere appearance of a conflict may be just as serious and potentially damaging as an actual distortion of objectivity. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts.

AAMC Guide

It is not possible to completely eradicate the potential for conflict of interest because there are certain rewards that are inherent in the structure of our research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship. For example, positive research results per se may contribute to opportunities for publication, promotion, tenure, grant renewals, and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. In a sense, these influences can be as much a source of conflict in the search for truth as interests of a pecuniary nature. But kept in perspective, such incentives are not inherently bad and are indeed the motivating forces for diligent scientists.

AAMC Guide

Challenges for institutions and IRBs

- Identify conflicts of interest (COI)
- Determine extent to which these COI may bias or appear to bias research
- Manage these COI to protect both the integrity of the research and the welfare of the research subjects
- Identify cases where management of COI is not possible and where the proposed research cannot be done.

Regulations and Guidance

- For institutions receiving federal funding for research, directly or indirectly, there are federal regulations defining the Institution's role in identifying and managing conflicts of interest
- These policies and procedures apply to all research
- Policies are still evolving at both the federal and institutional levels
- The policies for different agencies differ greatly
(We'll discuss the two examples of greatest relevance to IRBs and CTOs: the FDA and NIH)

FDA Guidance – investigator must disclose

- Compensation made to the investigator in which the value of compensation could be affected by study outcome
- A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement
- Equity interest in the sponsor of a covered study - ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices
- Equity interest in a publicly held company that exceeds \$50,000
- Significant payments of other sorts with a cumulative value of \$25,000 or more made by the sponsor to the investigator or made to the investigators' institution specifically to support activities of the investigator

FDA Guidance – who must disclose

- Investigator: Any listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects
- Spouse and dependent children of an investigator

FDA Guidance - disclosure requirements

When applying to the FDA for approval of a drug or device, the **applicant** must present the results of the research on which the application is based and **either** must certify that no conflicts of interest have occurred **or** must disclose the specific financial arrangements and the steps taken to minimize the potential for bias.

Investigators disclose to company

Company discloses to FDA when applying for approval of drug (may be long after research is done)

No role for institution, CTO, or IRB

NIH Guide Objectivity in Research: Definition of Conflict of Interest

Anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights).

- “Significant” if over \$10,000 or more than 5% ownership (whichever is less) for the investigator, spouse, and dependent children.
- Excludes salary from institution; honoraria for consulting and lecturing for non-profits, etc.

NIH: investigator's responsibilities

- Investigator: anyone who makes a significant contribution to the design, performance, or interpretation of the research
- Focus: financial ties of researchers to for-profit organizations
- Disclosure to institution: yearly and whenever there is a significant change in research or in potential conflicts

NIH: Institution's responsibilities

- Have written policies and procedures in place for disclosure and management of COI
- Inform investigators of policies, responsibilities, and regulations
- Solicit and review disclosures
- Ensure and certify the disclosures are current before research support is released for use
- Take appropriate action to manage, reduce or eliminate effects of conflicts of interest on research integrity
- Establish enforcement mechanisms
- Maintain appropriate records on disclosures and on management of COI
- Report to NIH as required

NIH Guide Objectivity in Research: IRB responsibilities

When Institutional Review Boards (IRBs) review specific protocols for the procedures to protect human subjects, the IRB must determine that:

- risks to subjects are minimized
- risks to subjects are reasonable in relation to the anticipated benefits
- selection of subjects is equitable
- informed consent will be sought from each prospective subject and appropriately documented

NIH Guide on Objectivity in Research: IRB responsibilities - continued

“While there is no regulatory requirement for IRBs to consider investigators’ financial conflict of interest, the protection of human subjects requires objectivity in communicating risks, selecting subjects, promoting informed consent, and gathering, analyzing and reporting data.”

NIH Guide on Objectivity in Research: IRB responsibilities - suggestions

- Make IRB members aware of the conflict of interest policies and procedures in their institution.
- Include a statement in the informed consent form that all clinical investigators comply with the institutional guidelines.
- Ask all investigators to complete a COI questionnaire.
- Provide instruction to IRB members on how to identify and respond to a perceived financial, academic or other conflict of interest.

So, the problem for those overseeing clinical research is that:

- It is clear that conflicts of interest can create real dangers and perceived problems.
- Regulations, guidance, and procedures from agencies are sometimes in conflict and sometimes hint at implicit expectations for Institutions and their research infrastructures, including CTOs and IRBs, without providing clear guidance.
- It is clear that CTOs, IRBs and ethicists will be among those held accountable when things go wrong.
- What do IRBs and CTOs need to do?

IRBs must consider whether conflicts of interest could affect the integrity of the research they oversee

- The recruitment process
- The ability of potential subjects to understand the implications and context of the research
- The integrity of the process of informed consent
- The safety of the subjects
- The design of the study
- The integrity of the performance of the research and of the interpretation and presentation of the results
- The ultimate value of the research

Some areas of concern

- Conflicts of Interest of investigators
 - PI
 - Other researchers
- Institutional Conflicts of Interest
- CTO Conflicts of Interest
- IRB Conflicts of Interest

Investigators

- Some clear guidance in this area
- IRBs need to work with institutional COI committees to set up procedures and to maintain communication about potential COIs.
- The problems before the IRB are different than those before the COI committee:
 - More specific
 - Focused on individual research protocols
 - Focused on research involving human subjects

Things to consider for clinical research projects with investigator COIs:

- Can the potential conflict be managed?
- Is disclosure of conflict to potential participants sometimes desirable? required? sufficient?
- Are additional safeguards needed?
 - Independent DSMBs
 - Independent analysis of data
 - Limited roles for some investigators
 - Exclusion of some investigators
 - Performance at a different institution
- Does the nature and structure of trial influence how important the COI will be?

Institutional Conflicts of Interest

- Evolving area – very little clear guidance
- Basic question: Is the institution able to review and oversee the research in an objective manner?
- Balanced, reasoned thought is needed
- No single answer
 - One extreme: Gelsinger case and IGT
 - Other extreme: Institution unable to do research with any company in its investment portfolio or any company in the retirement portfolios of its faculty and staff
 - **Neither extreme is appropriate**

IRB Conflicts of Interest

Conflicts of Interest of individual members

- Conflicts on individual protocols
- Conflicts with individual investigators
- Structural and reporting conflicts

- Financial conflicts of interest
- Other factors
 - personal or professional relationships
 - Strong beliefs or opinions
 - past experience which precludes objectivity

Conflicts of the IRB as an entity

- Are there protocols an IRB should not review?
 - Because of their reporting structure
 - Because of the potential perception of a conflict of interest by those outside the institution
 - Because pressure has been put on the IRB
 - Because of past interactions with investigator or sponsor which may unduly influence the panel
- What should the IRB and/or the Institution do if this problem arises?

Some Yale Policies on COI

- <http://www.yale.edu/provost/html/coi.html>
- Apply to all research
- Recognize special issues and concerns inherent in research involving human subjects
- Apply to all faculty, staff, students, *and others* who are responsible for the design, conduct or reporting of research
- Apply to certain administrators
- Apply to members of review committees that oversee research (HICs, IACUC, RSC, BSC, others)

Procedures

- Annual Disclosure of Potential COIs
- Updates of disclosure if needed when projects or significant interests change
- Review by Provost's Committee on COI
- Further discussions, inquiries if needed
- Management if needed - wide range of options
 - Structuring of research
 - Oversight committees, monitoring
 - Divestment
 - Prohibition of certain research projects

Policies include penalties for non-compliance

- Grants/contracts cannot be activated or renewed until COI issues are resolved
- Non-compliance during a research project can result suspension of project (this can necessitate reporting to the funding agency) and penalties up to and including termination of employment or legal action

HIC policies

- http://info.med.yale.edu/hic/policy/IRB_COI_policy.pdf
- Protocol-related COI disclosure required
- Somewhat different from Provost's COI form
 - Specific to a single protocol
 - No threshold for significance of financial interests
 - Incorporates additional elements of AAMC COI guidelines
 - Finder's Fees
 - Gifts

Focus of HIC interest in COI is narrow

- Focus is on the protection of the people who may become subjects in one specific study
- HIC may require that COI be considered in
 - Structure of that trial
 - Requirement for external DSMBs or analysis
 - Monitoring of consent process
 - Blinding
 - Role of participants (can include exclusion)
 - Information on informed consent form (disclosure of COIs to potential subjects)

Many implications for CTO

- There may be times when members of the CTO will be considered to be “engaged in research” and will need to file disclosures
- There may be times when members of the CTO have COIs related to specific projects that should be disclosed even if they are not “engaged in research”
- Multiple roles of CTO members may create conflicts
 - Mandate to develop research portfolio vs mandate to oversee research (Duke citation)
 - Effort spent in developing protocol may raise problems in reviewing its final form or overseeing it

- Many issues to think about when
 - Structuring research projects
 - Developing protocols
 - Developing consent forms, consent processes
 - Developing budgets and contracts
- Need to ensure that all disclosures have been filed and reviewed to avoid delays in activation of protocols and funding
 - HIC protocol-specific forms
 - Forms for Provost's COI committee

Management of COI continues during data acquisition, analysis and reporting

- Need to ensure that any management tools required by the HIC or COI committees are implemented before the research begins and that they remain in place and effective
- Need to ensure that COIs are managed during the research
 - Changes in interests
 - Changes in investigators
 - Annual updates

Summary of COI Issues

- Conflict of Interest is an evolving area of concern
- Many issues for investigators, institutions, CTOs, IRBs and individual IRB and CTO members to consider
- More questions than answers
 - Lofty questions of ethics
 - Legal questions
 - Practical questions of management and documentation
- One thing is clear: Research Organizations and their CTOs and IRBs will be increasingly asked to consider issues of conflict of interest and to decide how to manage, reduce, or eliminate their effect on the integrity of research involving human subjects and on the safety and welfare of the subjects