

# Long-Term Follow-Up in Gene Transfer Clinical Research

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# What is LTFU?

“...the collection of data on delayed adverse events in subjects who have been exposed to investigational gene therapy products.”

“When a gene therapy clinical trial presents long-term risks to human subjects, [the] trial must provide for long-term follow-up observations in order to mitigate those risks. Without such long-term follow-up observations, the study would expose the subjects to unreasonable and significant risk of illness or injury.” (cites 21CFR 312.42(b)(1)(i) and (b)(2)(i))  
--from FDA Guidance

Where did this idea come from?

# GT differs from drug or device

- May or may not have elimination PK— stable integration, prolonged expression is goal of some GT interventions
- Transgene expression not readily modulated (can't dial down or shut off)
- Effects can be delayed (months, years)
- Can affect others (contacts, offspring)
- More complex than we currently know

# Where did this idea come from?

- Asilomar 1975
- NIH Guidelines 1976
- Letter to RV vector sponsors 1993
- FDA “Gene Therapy Letter” 2000
- FDA Biological Response Modifiers Advisory Committee (BRMAC) 2000-2001
- Collaborative ASGT workshop 2004
- FDA Guidance 2005-2006

# BRMAC (October 2001)

“actual and/or hypothetical long-term risks of malignancies and/or hematologic, neurologic, or autoimmune diseases that may occur to participants”

- Risk-based (potentials to integrate and replicate, altered tropism, long latency)
- Cited latencies of 5-9 years for leukemia after treatment for Hodgkin's, and 10-15 years for relative risks of other cancers

# Malignancy risks

- Direct viral oncogenesis (HPV for cervical or head & neck cancers, others)
- Several possible mechanisms
- Subjects with cancer are typically exposed to many oncogenic therapies, so it may be hard to detect additional risks of gene transfer

# Hematologic risks

- Perceived threat to stem cells (e.g., HPC hematopoietic progenitor cell)—already self-replicating, range of potential harms
- Insertional oncogenesis in X-SCID trials
- Other mechanisms: parvovirus B19 and red cell aplasia, HIV and marrow suppression

# Neurologic risks

- Concern over insidiousness of possible harm—profound cell loss before detection of clinical harm (e.g., Parkinson’s)
- “neuronal components of the mature CNS do not appreciably regenerate”
- Sustained exposure to low-grade damage could have serious impact

# Autoimmune risks

- Concerns mainly theoretical, based on projections from known mechanisms
- Many oncology products designed to work at least partly through immune stimulation
- Cancer cell death exposes “self” antigens to immune system

# What do the regulations say?

- NIH Guidelines

[http://oba.od.nih.gov/oba/rac/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm)

- FDA Regulations

- FDA Guidance on Long-Term Follow-Up for Gene Transfer

<http://www.fda.gov/CBER/gdlns/gtclin.htm>

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>

# NIH Guidelines and LTFU

## Appendix M-III: Informed Consent

- M-III-B-2: Specific Requirements of Gene Transfer Research
  - Scientific rationale: “To permit evaluation of long-term safety and efficacy of gene transfer...”
  - Ethical rationale: “subjects should be informed...[of] the harms and benefits experienced by other[s], and any long-term effects that have been observed.”

# Who is responsible?

## Responsibilities of the Institution

- ensure that PI addresses all aspects of Appendix M IV-B-1-f
- ensure compliance with NIH Guidelines IV-B-1-g
- report any significant research-related illnesses IV-B-1-j

# Who is responsible?

## Responsibilities of the IBC

- ensure that PI addresses all aspects of Appendix M IV-B-2-a-(1) and IV-B-2-b-(1)
- ensure compliance with all surveillance...and adverse event reporting requirements [of] the NIH Guidelines IV-B-2-b-(1)

# Who is responsible?

## Responsibilities of the PI

- ensure that the reporting requirements are fulfilled IV-B-7
- report any significant research-related illnesses to IBC, NIH OBA, etc. IV-B-7-a-(3)
- ensure that all aspects of Appendix M have been appropriately addressed IV-B-7-b-(6)

# FDA approach 2001-2006

2000-2001: Biologic Response Modifiers Advisory Committee (BRMAC) meetings

2004: pre-ASGT workshop

LTFU should be specific and risk-based; some subjects not suitable due to high short-term mortality, poor health, or exposure to mutagens

See published summary; workshop materials archived on the ASGT website Mol Ther. 2004 Dec; 10(6): 976-80.

[www.asgt.org/archived\\_course\\_materials/workshop04/workshopmaterials.php](http://www.asgt.org/archived_course_materials/workshop04/workshopmaterials.php)

2006: “Guidance for Industry” (2005 draft; Nov 2006 final)

# FDA Guidance on Long-Term Follow-Up for Gene Transfer

Typical follow-up before the Guidance:  
annual exams for at least 5 yr, then annual queries for 10 years

“Contains non-binding recommendations”  
(but says “must”)

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>

# FDA LTFU Guidance

1. recommended methods to assess risk of delayed AEs
2. recommended methods to assess likelihood that LTFU will provide scientifically meaningful information
3. specific advice regarding duration and design of LTFU

# FDA LTFU Guidance

Cites four risk factors for delayed AEs

1. Persistence of viral vector
2. Integration of genetic material into host genome
3. Prolonged transgene expression
4. Altered expression of host genome

# FDA LTFU Guidance

**V-D-4. Amendments to Your Clinical Protocol:** If clinical data suggest that your product is not associated with delayed risks, you may want to consider changing the clinical protocol regarding long-term follow-up of study subjects. However, before implementation of this change, you must submit to FDA a protocol amendment to your IND indicating the relevant changes (21 CFR 312.30(b)(1), (d), and (e)).

Who benefits?

# Arguments in favor of appropriate LTFU

- Ethical
- Scientific
- Regulatory

# The real world...

- It's expensive
- It's not glamorous
- Bad things happen to nice companies
- You get what you pay for
- Who is asking for the results? Who is doing organized data synthesis or meta-analysis?
- Poorly integrated regulatory environment
- No one's priority

# Real World: Protocols

PLAN: “All randomized patients will be followed for the duration of their life for survival and potential long-term effects of therapy .”

OUTCOME: “[Sponsor] retains the right to terminate the study...at any time.”

# Real World: Protocols

PLAN: “All patients enrolled in the study will be followed for survival until death. Every attempt should be made to ascertain survival status for each patient on a monthly basis for twelve months, and every three months thereafter.”

OUTCOME: “Study Termination For reasonable cause, with written confirmation, either the Investigator or [Sponsor] may terminate the study at a given center or all centers. Conditions that may warrant termination include, but are not limited to....

# Another strategy

- Write the LTFU into a separate registry protocol, in which no rDNA is directly involved.
- Modify or terminate that protocol.

Reliance on FDA, IRB (like post-marketing surveillance)? What role for NIH, IBC?

## PI comments (I)

“the sponsor went into bankruptcy several years ago and closed its doors. We are not following any patients...in fact, the NCI has handed over the study to a new company... that is not collecting follow-up information either.”

## PI comments (II)

“We have rejected a protocol in the past where we were concerned about the sponsor going bankrupt during what could have been a costly follow up period.”

# Sponsor close-out letter (I)

“Although the protocols were not amended to reflect this [early closure], it is not standard industry practice to formally amend a protocol when a trial is prematurely terminated to reflect all changes to patient monitoring....”

## Sponsor close-out letter (II)

“As a reminder, the long-term follow-up aspect of the protocol mandates that all subjects be contacted on an annual basis for the next two years.”

# “Study closure” depends on perspective

subject: stop dosing; stop visits??

sponsor: stop LTFU, stop monitor visits, stop payments, stop annual reports, close IND, reassign staff

PI: stop AE reporting, dispose product, notify IRB, archive protocol, reassign staff

IRB: receive study closure report, stop activity

IBC: no product on-site, no dosing, LTFU completed

FDA: close IND

NIH: ummm...

# FDA Study Closure

21 CFR 312.38

“If an IND is withdrawn, FDA shall be so notified, all clinical investigations under the IND shall be ended...

CBER SOPP 8206: deals with the sponsor going out of business—it doesn't help here

<http://www.fda.gov/CbER/regsopp/8206.htm>

# NIH Study Closure

- Nothing in NIH Guidelines
  - Nothing in IBC FAQs
  - Nothing in GeMCRIS
- 
- There is something...

# NIH Study Closure

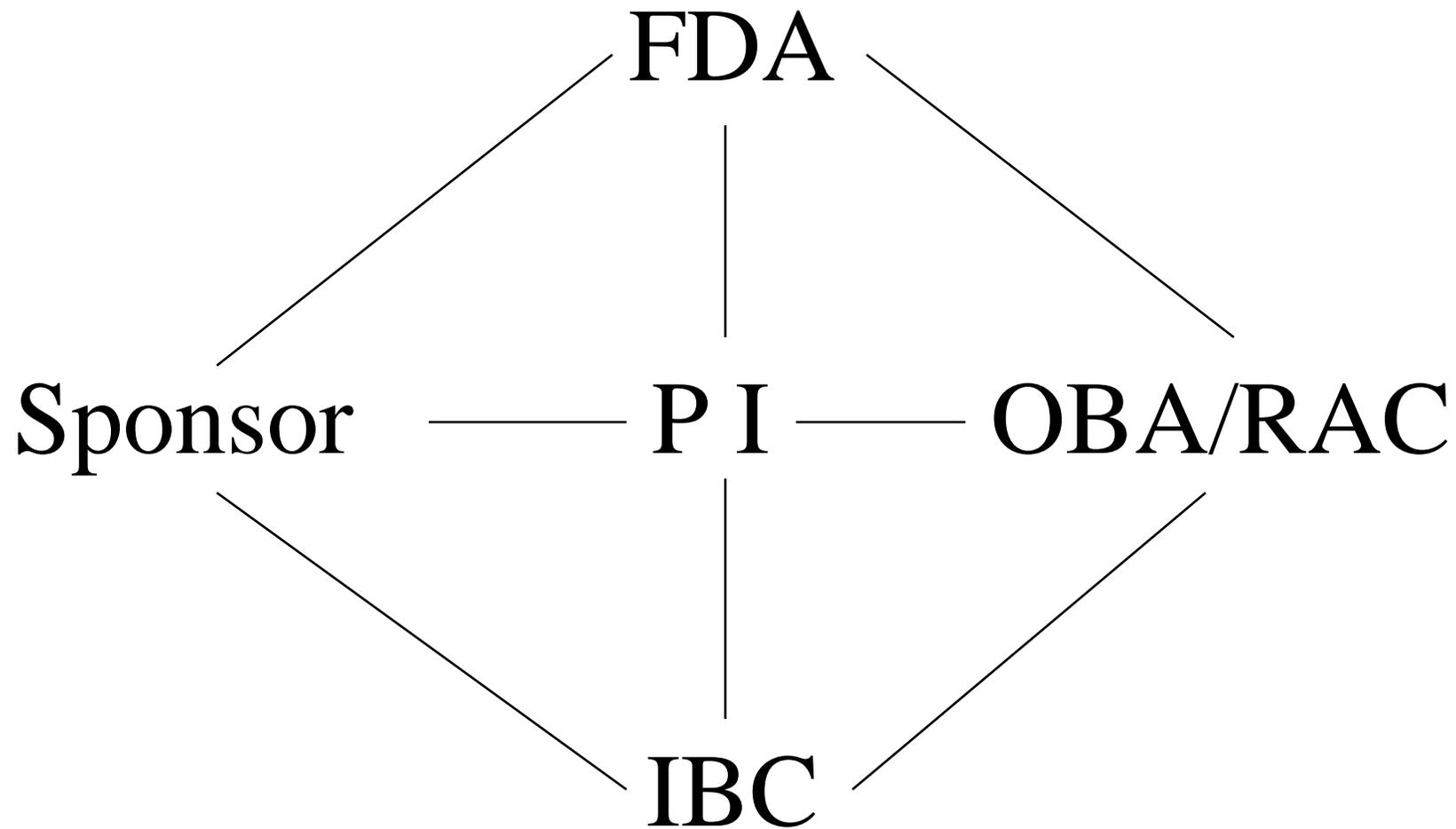
“When all research-related interventions or interactions with human subjects have been completed, and all data collection and analysis has been finished, then the human subjects research study has been completed.”

NHLBI Clinical Research Guide

[http://www.nhlbi.nih.gov/crg/studyclosure\\_index.php](http://www.nhlbi.nih.gov/crg/studyclosure_index.php)

# NIH Study Closure...There's More

- NIH compliance relationship is with institution, IBC, and PI (not sponsor)
- PI should follow LTFU procedures described in the IBC-approved protocol (or make case to modify the research)
- IBC and others [FDA, IRB] have authority to determine appropriateness of LTFU plan
- At approval, IBC should anticipate possible early closure by sponsor, and consider adequacy of contingency plans.



# Observations

- Scientific and social values of LTFU
- Ethical duty to past and future subjects
- a better support framework
  - Distribution of benefits and burdens is a matter of policy-setting
  - Funding (not all LTFU is of equal value)
  - Clarify regulatory environment

# Possible Solutions

- Sponsors: address LTFU contingencies in protocol design stage and written protocol documents
- Investigators: evaluate LTFU (duration, cost, etc.) and negotiate with Sponsor to assure ability to implement the specified LTFU measures; prepare contingency plan to present to IBC, IRB, FDA
- Institutions: support PIs
- NIH, FDA: clarify and harmonize regulatory environment, provide national support for GT LTFU

# Thank you

To NIH OBA who are always willing to help and answer questions.

To the pioneers who developed our current ethical and oversight framework

To gene transfer researchers and sponsors who have talked with me about this topic