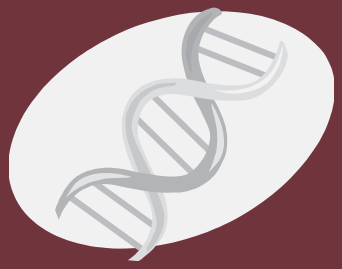

Informed Decisionmaking in Gene Transfer Research

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ASGT May 30, 2007

Ethical Issues in GTR: Challenges

- disease range: from monogenic disease to cancer
- risk range: from germline transmission to vector toxicity
- lack of good animal models
- hard to predict dose-dependent safety and efficacy
- variability in diseases and interventions
- potential for permanent changes; long-term risks of harm
- heightened uncertainty; complex history
- “irrational exuberance” about potential benefits?
- some special societal (even metaphysical?) concerns

Ethics Meets Science in GTR

- Does preclinical evidence support research safety and validity?
- Does the study have sufficient value (safety, fairness, payoff)?
- Guidelines, monitoring, and long-term follow-up
- Detecting rare events in animal and human studies
- Collection and testing to monitor shedding, biodistribution, vertical transmission risk
- Ethics of study design
- Assessing subject selection & consent form
- Minimizing uncertainty and risks of harm
- Discussing uncertainty and reasonable expectations

Moving to Clinical GTR

- Has enough preclinical information been collected so that the only reasonable way to learn more is to move to humans?
- Has enough been done to reduce the risks of harm to humans, and to maximize the likelihood that the gene transfer intervention will ultimately show benefit in humans?
- Has the point of irreducible uncertainty been reached?
- Is the amount of irreducible uncertainty small enough that it is fair to subjects to ask them to become involved in the research?

Selection of Patients as Subjects Should Reflect Research Goals

- minimizing risks of harm -- for which subjects can the risks of the intervention be meaningfully minimized?
- maximizing contribution to generalizable knowledge -- from which subjects can maximally useful data (amount, meaning, interpretability) be obtained?
- both goals must be met; they can conflict; this presents challenging ethical/design questions.

Who Should Be First?

- **Should subjects be more like "healthy volunteers"?**
  - adults with relatively stable disease
  - informed and unpressured decisions about participation
  - possible to minimize risks of harm
  - reliable and interpretable data
- **Should subjects be more like the sickest patients?**
  - most often asked in early-phase trials (e.g., oncology)
  - treatment possibilities exhausted
  - not tempted to forgo a "bird in the hand"
  - may value potential benefits more, or risks less

Risks of Harm

- **Historical Fears**
- **insertional mutagenesis**
- **germline effects**
- **Speculative Harms?**
- **“I wouldn’t do it, but it can’t hurt, so why not?”**
- **Materialized Harms**
- **viral vector effects (adenovirus, AAV)**
- **XSCID leukemias**
- **positive PCR in semen**

Benefit: Types & Dimensions

- **Direct Benefit**
  - resulting from receipt of the intervention(s) being studied
- **Dimensions of Direct Benefit**
  - ***Nature***
    - clinical endpoint?
    - OR: surrogate endpoint, or “empty” statement?
  - ***Magnitude***
    - **size** (improvement? cure?)
    - **duration** (temporary? permanent?)
  - ***Likelihood*** (affected by dosage group, design, number of subjects?)
- **“Inclusion” Benefit**
  - resulting from being a subject, independent of the studied intervention (e.g., close monitoring, extra free testing or treatment)
- **Aspirational Benefit**
  - to society, to science, to future patients

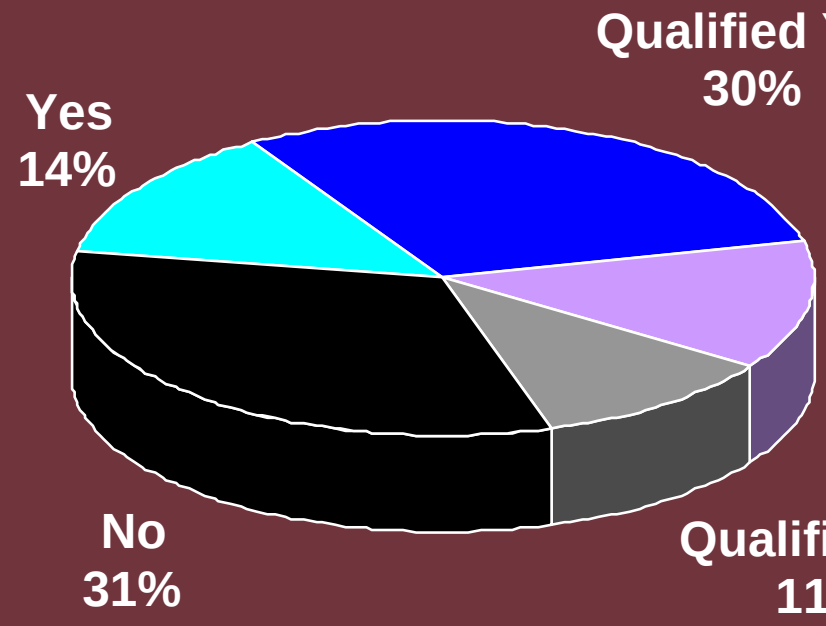
Social Construction of Benefit in Gene Transfer Research

- Gail E. Henderson, PhD, UNC
- Nancy M. P. King, JD, WFU
- Larry R. Churchill, PhD, VU
- Arlene M. Davis, JD, RN, UNC
- Daniel K. Nelson, MS, UNC
- Benjamin S. Wilfond, MD, UW
- Catherine R. Zimmer, PhD, UNC
- Michele M. Easter, MA, UNC
- Barbra B. Rothschild, MD, UNC
- More information about GTR and our project is available on the Benefit in Gene Transfer Research Project website: http://socialmedicine.med.unc.edu/scob/

PIs' Views on Likelihood of Direct Medical Benefit (N=37)

"We expected an immune response based on pre-clinical studies."

"It certainly was in the realm of possibility"



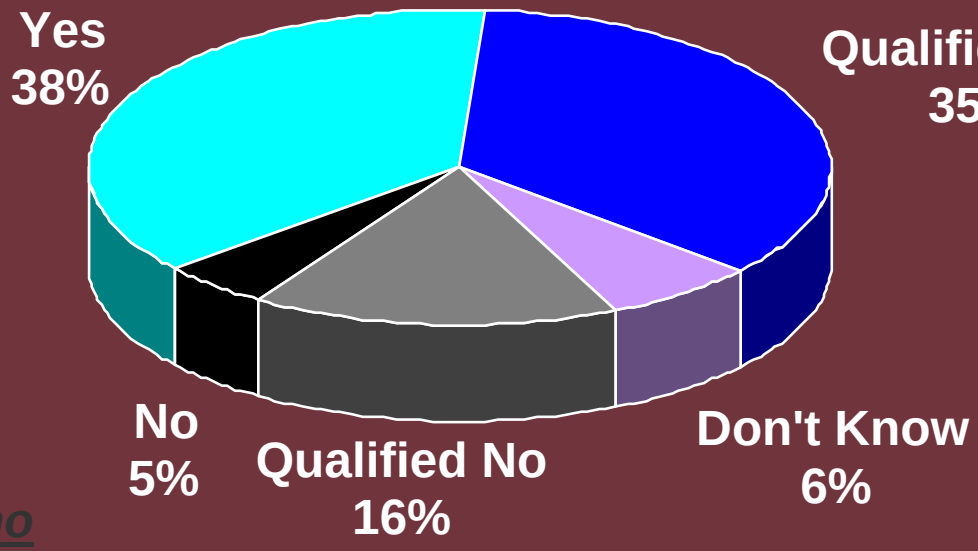
"This is a safety trial not an efficacy trial."

"…conceivable but not powered to detect."

Subjects' Views on Likelihood of Direct Medical Benefit (N=62)

"… the data led me to expect it would help."
"[PI name] told me it would help..."

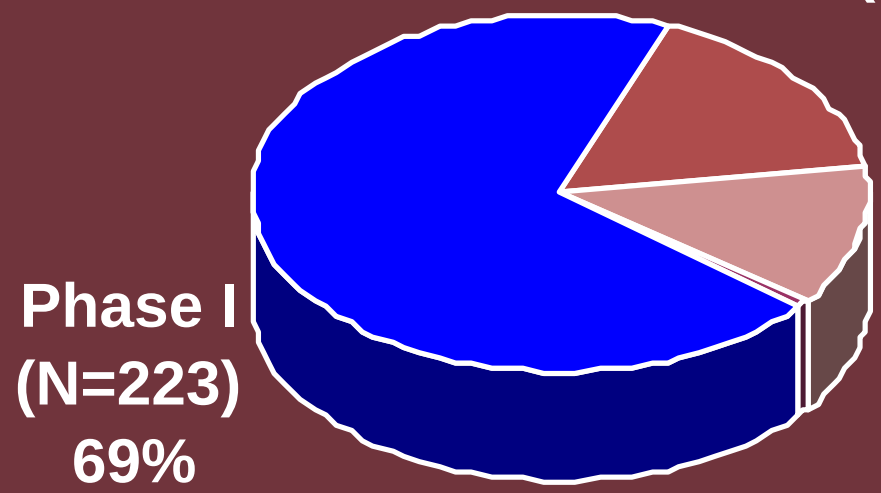
"… hoping it could"



"Absolutely no because that's what they told me."

"I'm sure in the back of my mind I hoped but I didn't really expect it."

Phase (N=321 Total)



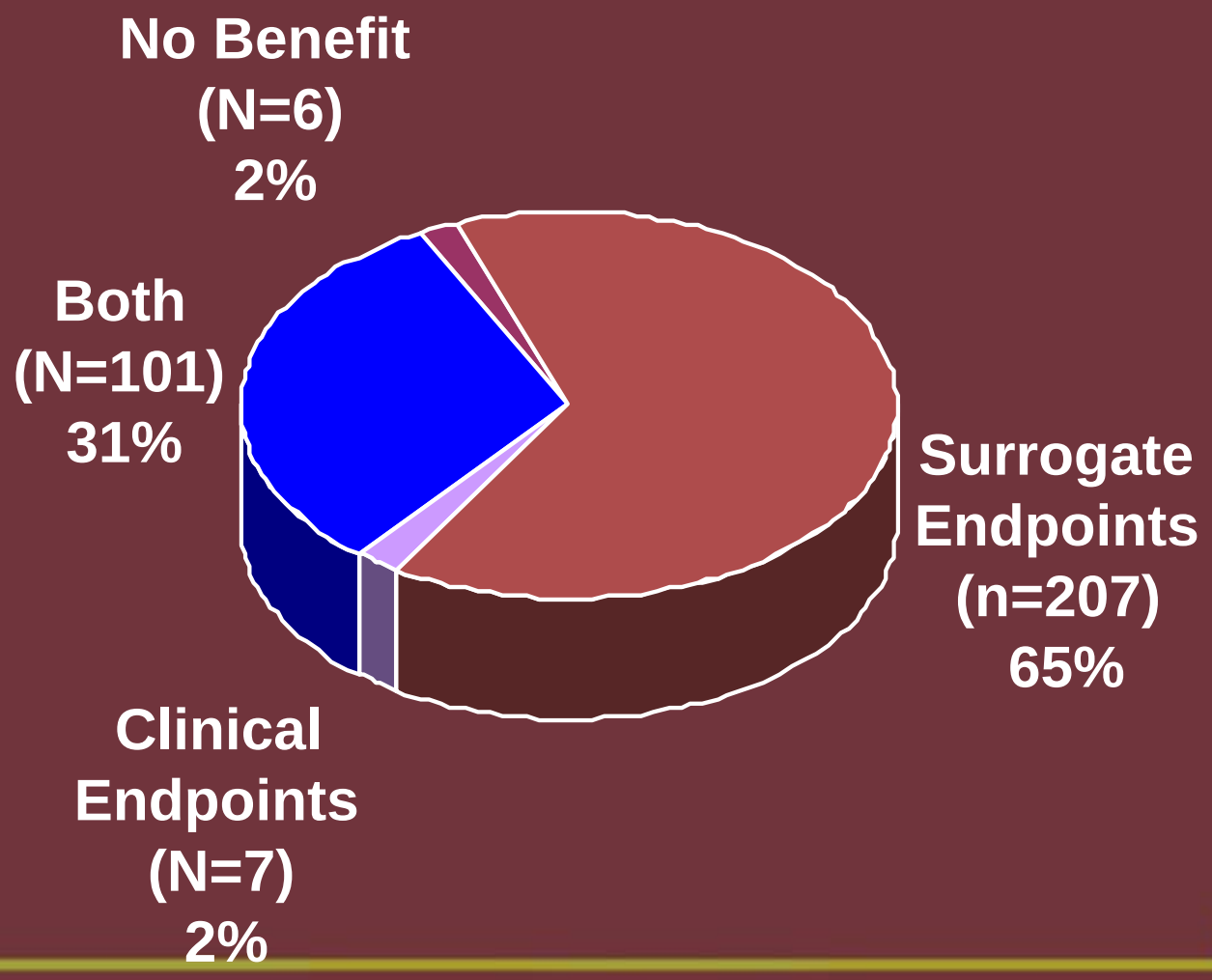
Phase I-II
(N=54)
17%

Phase II
(N=41)
13%

Phase III
(N=3)
1%

Phase I
(N=223)
69%

Does CF Offer Direct Benefit to Subjects?



Phase I Pilot Trial of [X] on…Lung Cancer

Purpose: It has been explained to you that you have…lung cancer that requires radiation therapy to the chest to relieve symptoms. You have been invited to participate in this research study. This study involves treatment with an experimental agent called [X] which is a modified common virus designed to carry a normal copy of the tumor suppressor [Y] into tumor cells. Tumor cells are often killed or their growth is suppressed when this gene is put into them, and the hope is that we can improve your symptoms and prolong your life with this treatment. [X] will be given to you by bronchoscopy or through the ski) to a portion of your lung affected by your tumor. The purpose of this study is to determine whether this procedure is safe and to evaluate the effect of this treatment on your lung cancer.

Benefits: It is not possible to predict whether or not any personal benefit will result. You have been told that, should your disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest, or should your physicians feel that this treatment is no longer in your best interest, the treatment would be stopped. Further treatment would be discussed.

Ambiguous Expectations?

PI: “Oh, it’s a long shot. It’s a long shot.”

Q: “If you were just to say yes or no what would you say?”

PI: “Ah that’s tough, that’s actually, I’m really conflicted about that. I guess if you really push me, I’d have to say no, but I would like to say yes, but I don’t think that would be honest at this point. It’s a little bit too early… to work out.”

Q: “I can also punch here ‘don’t know’.”

PI: “Well, no, I don’t know. Nobody knows.”

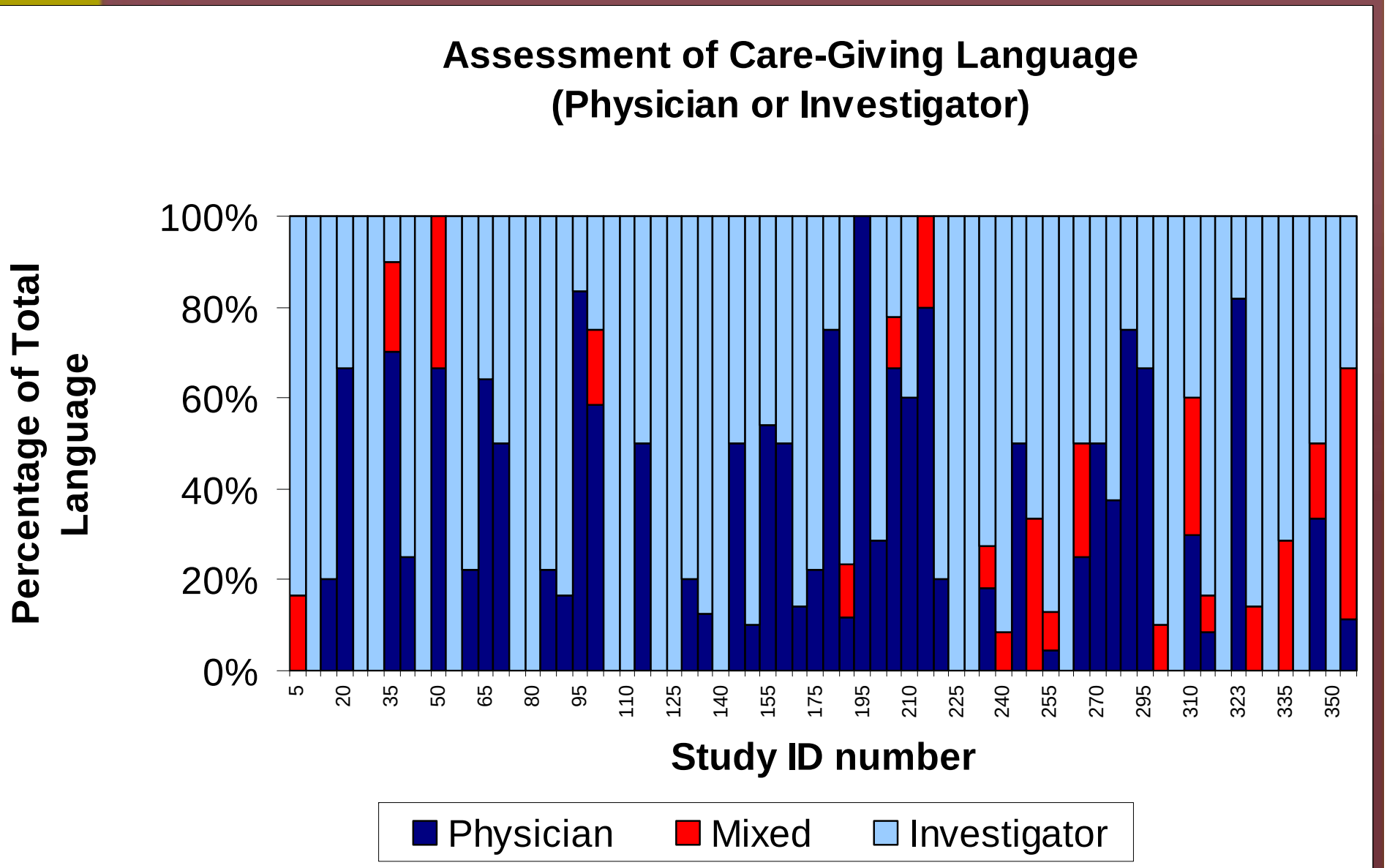
Q: “Would you like to answer that instead of yes or no?”

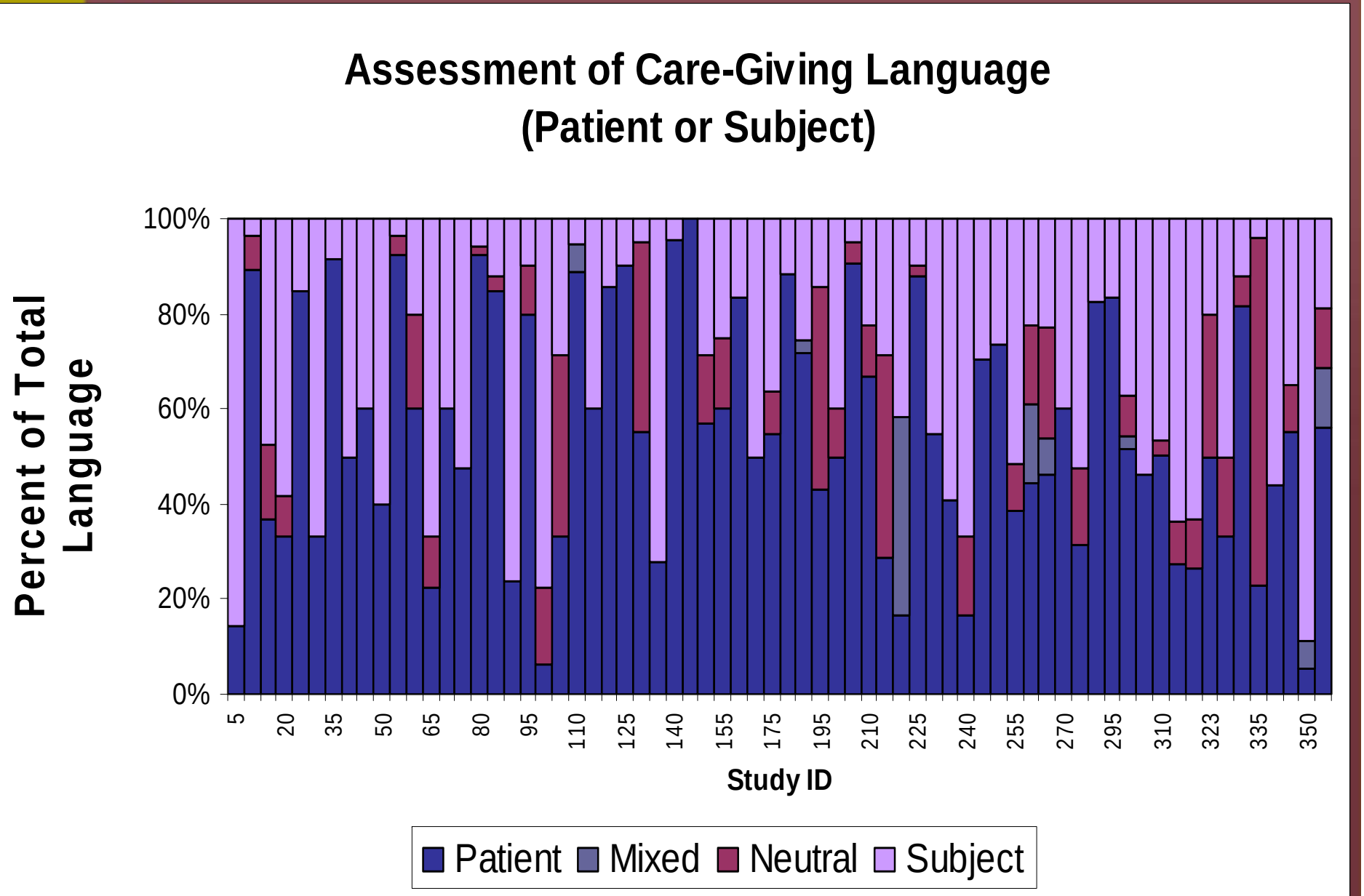
PI: “No I’ll put no. It’s the moral response.”

Assessment of Terms in CFs

In a systematic sample of 68 GTR consent forms, we counted and grouped *types of terms:*

- **for *investigator*:**
  - investigator, study doctor, or doctor
- **for *subject:***
  - patient, patient-subject, person, or subject
- **for *experimental intervention*:**
  - gene transfer intervention, study treatment, neutral (e.g., “gene shot” or ACRONYM), or treatment


Assessment of Care-Giving Language
(Physician or Investigator)
Percentage of Total Language
100%
80%
60%
40%
20%
0%
5
20
35
50
65
80
95
110
125
140
155
175
195
210
225
240
255
270
295
310
323
335
350
Study ID number
Physician
Mixed
Investigator


Assessment of Care-Giving Language
(Patient or Subject)
Percent of Total Language
100%
80%
60%
40%
20%
0%
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20
35
50
65
80
95
110
125
140
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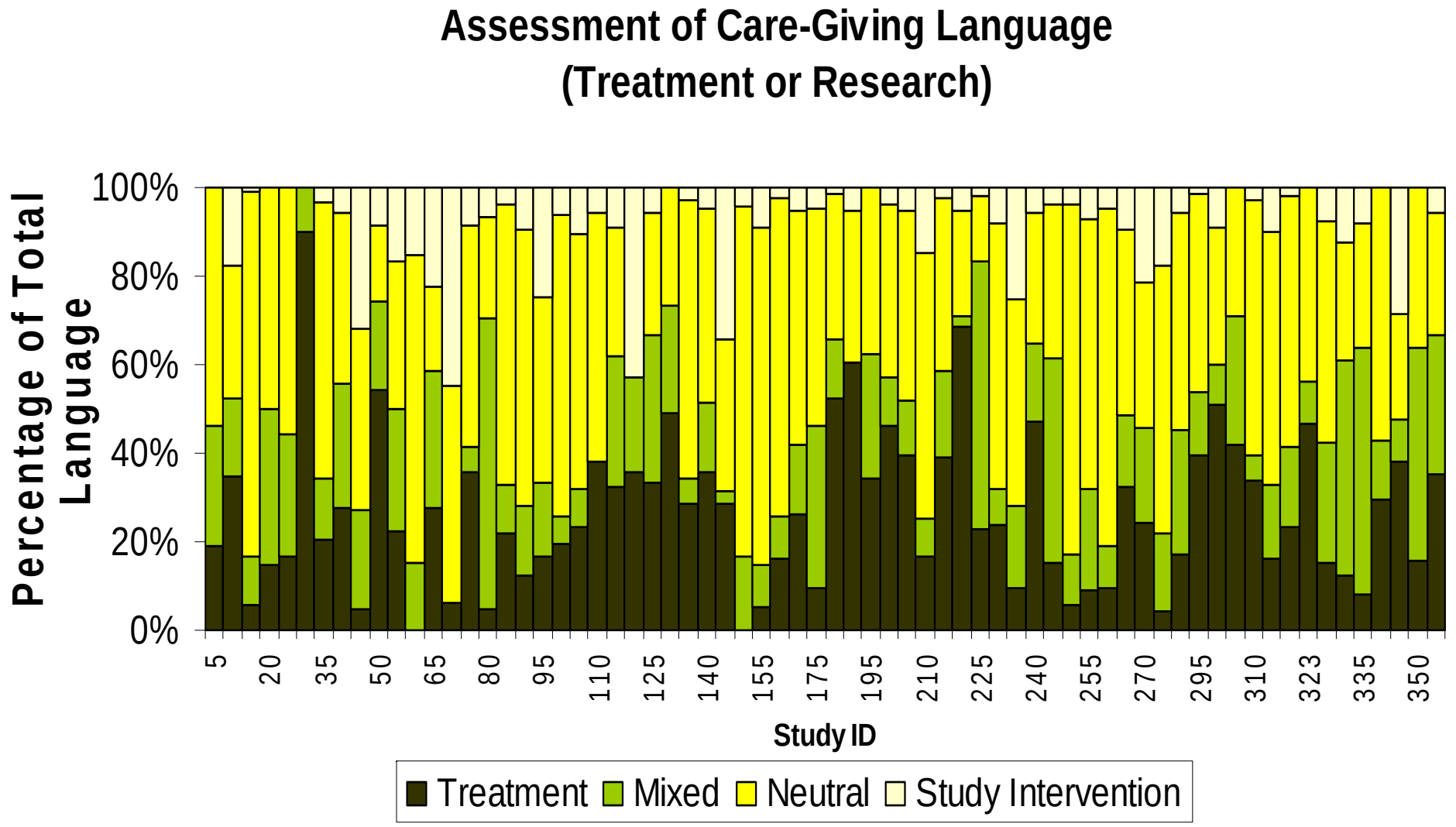
240
255
270
295
310
323
335
350
Study ID
Patient
Mixed
Neutral
Subject


Assessment of Care-Giving Language
(Treatment or Research)
Percentage of Total Language
100%
80%
60%
40%
20%
0%
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80
95
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125
140
155
175
195
210
225
240
255
270
295
310
323
335
350
Study ID
Treatment
Mixed
Neutral
Study Intervention

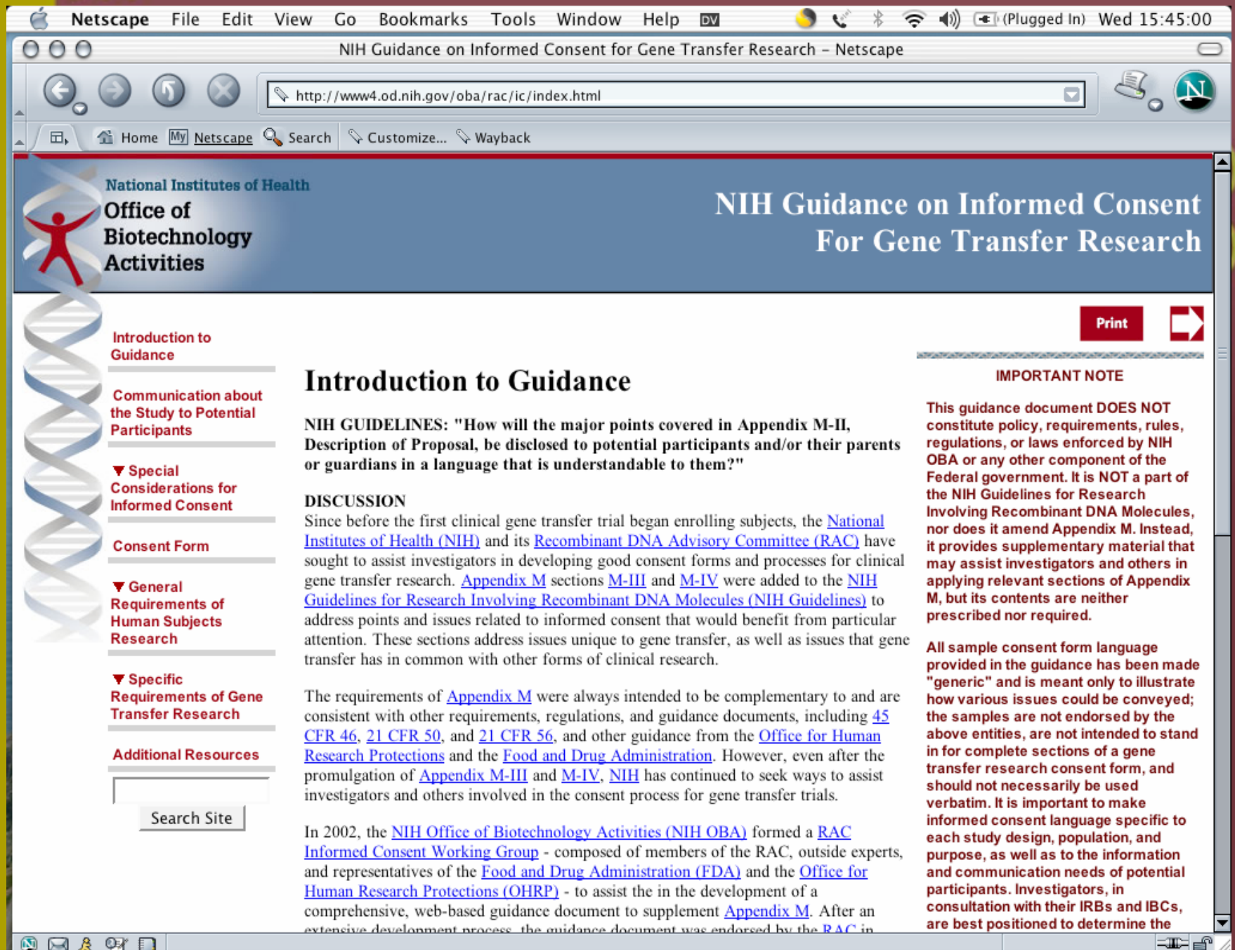
What's Wrong With This Headline?

"Gene Therapy Used to Treat Patients With Parkinson's", by Denise Grady and Gina Kolata, The New York Times, August 19, 2003.

- Story ran the day after the first subject in this phase I trial received the experimental intervention
- "Gene transfer" is the correct term
- It is not a treatment
- He is not a patient

NIH Guidance: Informed Consent for Gene Transfer Research

- Organized according the sections of Appendix M-III and M-IV of the NIH Guidelines
- Each section contains:
  - Text of relevant section of Appendix M
  - Discussion
  - Main Points sidebar box
  - Sample and Problematic Language sidebar box
  - Tools and Background Resources sidebar box
- The Document "NIH Guidance on Informed Consent in Gene Transfer Research" is available on the OBA website: http://www4.od.nih.gov/oba/rac/ic/index.html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NIH Guidance on Informed Consent for Gene Transfer Research - Netscape
http://www4.od.nih.gov/oba/rac/ic/index.html
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National Institutes of Health
Office of Biotechnology Activities
NIH Guidance on Informed Consent For Gene Transfer Research
Print
Introduction to Guidance
Communication about the Study to Potential Participants
Special Considerations for Informed Consent
Consent Form
General Requirements of Human Subjects Research
Specific Requirements of Gene Transfer Research
Additional Resources
Search Site
Introduction to Guidance
NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"
DISCUSSION
Since before the first clinical gene transfer trial began enrolling subjects, the National Institutes of Health (NIH) and its Recombinant DNA Advisory Committee (RAC) have sought to assist investigators in developing good consent forms and processes for clinical gene transfer research. Appendix M sections M-III and M-IV were added to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) to address points and issues related to informed consent that would benefit from particular attention. These sections address issues unique to gene transfer, as well as issues that gene transfer has in common with other forms of clinical research.
The requirements of Appendix M were always intended to be complementary to and are consistent with other requirements, regulations, and guidance documents, including 45 CFR 46, 21 CFR 50, and 21 CFR 56, and other guidance from the Office for Human Research Protections and the Food and Drug Administration. However, even after the promulgation of Appendix M-III and M-IV, NIH has continued to seek ways to assist investigators and others involved in the consent process for gene transfer trials.
In 2002, the NIH Office of Biotechnology Activities (NIH OBA) formed a RAC Informed Consent Working Group - composed of members of the RAC, outside experts, and representatives of the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) - to assist the in the development of a comprehensive, web-based guidance document to supplement Appendix M. After an
IMPORTANT NOTE
This guidance document DOES NOT constitute policy, requirements, rules, regulations, or laws enforced by NIH OBA or any other component of the Federal government. It is NOT a part of the NIH Guidelines for Research Involving Recombinant DNA Molecules, nor does it amend Appendix M. Instead, it provides supplementary material that may assist investigators and others in applying relevant sections of Appendix M, but its contents are neither prescribed nor required.
All sample consent form language provided in the guidance has been made "generic" and is meant only to illustrate how various issues could be conveyed; the samples are not endorsed by the above entities, are not intended to stand in for complete sections of a gene transfer research consent form, and should not necessarily be used verbatim. It is important to make informed consent language specific to each study design, population, and purpose, as well as to the information and communication needs of potential participants. Investigators, in consultation with their IRBs and IBCs, are best positioned to determine the

Informed Consent Guidance: Study Purpose

- You were asked to be in this study to help the investigators learn more about the type of disease you have. The investigators will try to keep the risks of harm to you from being in the study as low as possible. They believe that being in the study will not keep you from getting any treatments you may need for your disease.

--NIH Guidance on Informed Consent for Gene Transfer Research, http://www4.od.nih.gov/oba/rac/ic/

Informed Consent Guidance: Study Purpose cont'd

- This study will enroll people with your disease [CHOOSE WHICHEVER APPLIES]

- Whose disease has been treated unsuccessfully by all standard means
- Who will continue to receive standard treatment
- Who can probably put off standard treatment during the study
- Who can probably stop or change standard treatment during the study

Informed Consent Guidance: Direct Benefit

- Generic benefits statements, such as "You may or may not benefit from being in this study," or "Personal benefit cannot be predicted or guaranteed," do not provide sufficient meaningful information, particularly in early-phase studies.
- Investigators should distinguish between the ultimate goal of the line of research, the endpoints of the current study, and potential benefits to participants from the gene transfer.

Surrogate Endpoints

- Surrogate endpoints should not be described as benefits unless there is a well-established link to a clear health benefit.
- Investigators should discuss the clinical benefits that potential subjects may be hoping for, in order to explain clearly what expectations are reasonable and why, and what expectations are not reasonable and why.

Potential Benefit by Phase

- Uncertainty about the likelihood of direct medical benefit from the gene transfer intervention should always be mentioned.
- What is known about the potential benefits, if any, of a gene transfer intervention in a given study depends on the design and phase of the study and available evidence. Potential benefits discussions should be design-specific.
- Information about prior experience and its limitations should be presented in ways that can best inform decision-making about participation. Previous experience related to potential benefits in animal and human studies may be relevant if the meaning and limitations of the findings are carefully described.

More on Potential Benefit by Phase

Phase I:

- The mere hope that the intervention will be therapeutic is not sufficient justification for saying that direct medical benefit is possible.
- Depending on existing data, study design, and power, it may be most accurate to say that direct medical benefit is unlikely, or that there will be none.

Phase II:

- The consent form may include descriptions of potential direct medical benefit discovered in Phase I.
- It should be acknowledged that the extent of experience is limited.
- It is inappropriate to encourage expectations of medical benefit.

Informed Consent Guidance: Societal Benefit

- Many gene transfer consent forms fail to mention benefit to society.
- Potential subjects should be told that early phase studies are designed for scientific purposes and that those who participate in these studies may extend benefit to future patients by helping to advance scientific and medical knowledge.
- Especially in early phase trials, it is appropriate to say that the primary purpose of the study is to produce benefits to society.
- Distinguish clearly between benefits to society and potential benefits, if any, to subjects.

Informed Consent: Recommendations

- Keep consent forms simple & clear
- Avoid vagueness & inconsistency in use of terms
- Present benefit to society as the sole or primary goal of clinical research
- Describe study design (especially dose escalation) to help subjects distinguish research from treatment
- Describe direct benefit explicitly, including limits
- Use caution in offering study endpoints as potential direct benefits:
  - Describe as measurement goals only, unless
  - Clearly linkable to reasonably expected potential clinical benefits
- Distinguish ***hopes*** from ***reasonable expectations*** about research participation