

Informed Consent in Gene Transfer Research: Lessons for Early-Phase Clinical Trials

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Social Construction of Benefit in Gene Transfer Research

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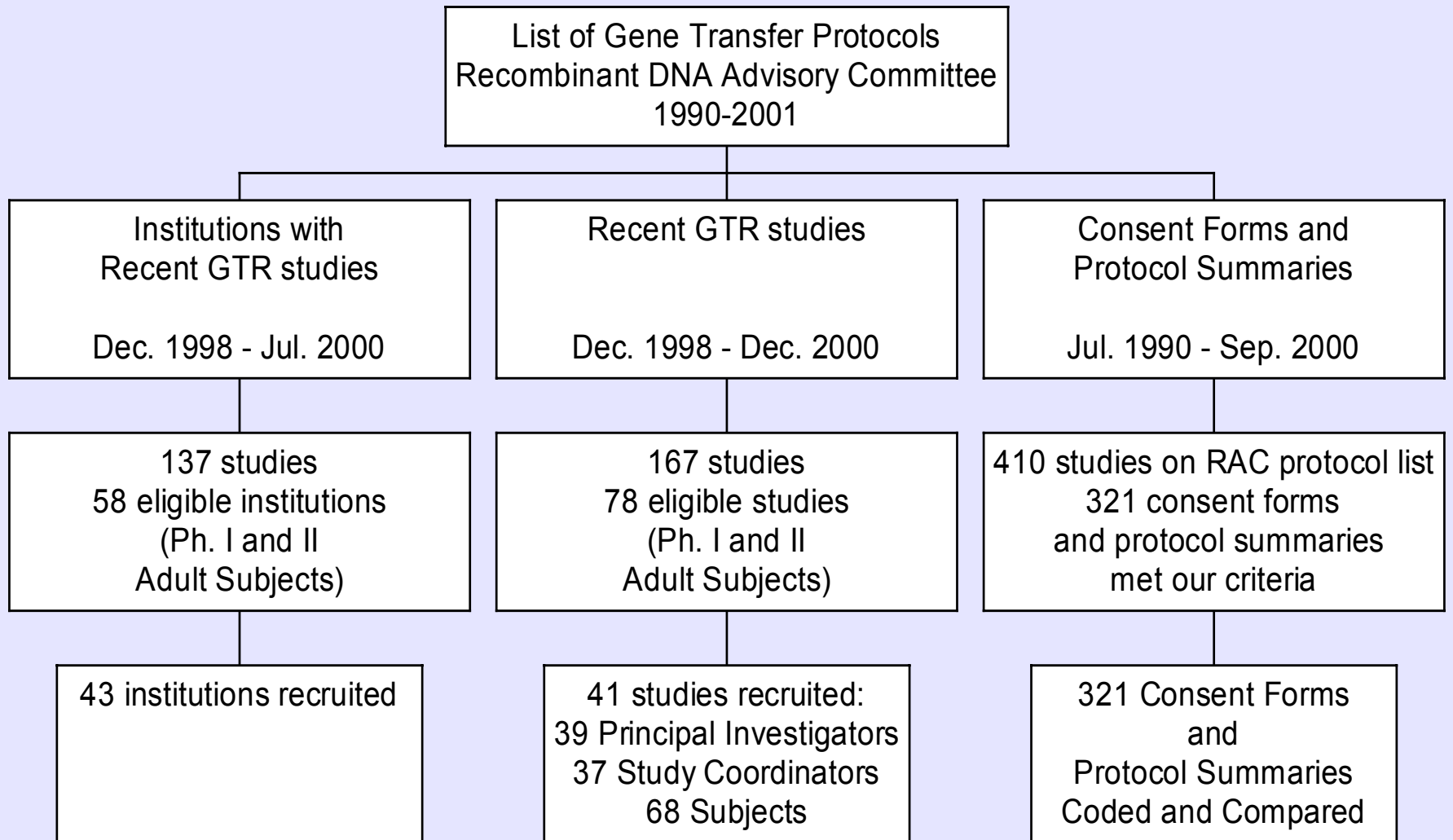
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Social Construction of Benefit in Gene Transfer Research (GTR)



Therapeutic Misconception/ Mis-estimation

Previous studies have focused on subjects in psychiatry and oncology trials

e.g., Daugherty et al. (2000) found that 90% of 144 phase I oncology subjects said that they “will get medical benefit from the treatment in this study”

Why Benefit in GTR?

- Most GTR is oncology research (where informed consent is most studied).
- Most GTR is early-phase research (which faces the greatest informed consent challenges).
- More oversight in GTR should mean better consent forms/process.
- GTR's unique social/scientific context may affect expectations.

Benefit: Types & Dimensions

- **Direct Benefit**

- resulting from receipt of the intervention(s) being studied

- **Dimensions of Direct Benefit**

- *Nature* (clinical endpoint?)
- *Magnitude*
 - **size** (improvement? cure?)
 - **duration** (temporary? permanent?)
- *Likelihood* (affected by dosage group, design, number of subjects?)

- **“Inclusion” (Collateral) 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

Nature of Direct Benefit

- **Contentless (no nature information)**
 - “you may or may not benefit”; “personal benefit not guaranteed”
- **Surrogate endpoints (statistical ‘stand-ins’)**
 - tumor shrinkage; lowered PSA; increased % circulating Factor VIII; growth of new blood vessels; increased CD4+ count
- **“Vague clinical” endpoints (perceptible but not specific)**
 - feel better; improved blood flow; relief of symptoms; improve quality of life; improve immune system function
- **Clinical endpoints (clearly perceptible)**
 - cure; remission; less pain in leg; live longer; improved breathing; fewer bleeding episodes; fewer infections
- *We coded only those endpoints offered as direct benefits*
- *We coded surrogate and “vague clinical” endpoints together*

GTR Interviews and Analysis

- **Telephone interviews** July 2000-July 2002 with
 - 39 investigators
 - 37 study coordinators
 - 68 subjects
 - from 41 GTR trials
- **Direct Medical Benefit Questions:**
 - “Did you expect that getting the gene transfer would improve your condition or help make you better? Would you say yes or no?”
 - “Why did you expect that it [would/ would not] improve your condition or help make you better?”
 - “Did you expect that the gene transfer intervention in this study would have a direct medical benefit for your subjects?”

What Did Subjects Expect/ Hope For?

“Not lose my foot”

“It would decrease the amount of bleeds”

“Get rid of this cancer in my prostate”

“I expected it to help”

“Help the blockages in my heart”

“If it works, I won’t need radiation”

“I was hoping it would have an effect”

What Did PIs Expect/Hope For?

“Tumor shrinkage”

“Have the vector produce factor”

“Boost the immune system”

“Stimulate anti-tumor response”

“Grow new blood vessels”

“ [C]ancer cells will be exposed to the gene and take up the gene...”

“Keep the tumor localized”

“Longer survival”

“Eliminate the pain that they are having”

“Decrease severity of infections”

“Restore normal circulation”

“Avoid amputation”

“Reduce complications of chemotherapy”

“Decrease symptoms”

“Clinical benefit,” “positive results,” “therapeutic option”

Some Found It Hard To Answer

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.”

Consent Form Coding & Analysis

Coders:

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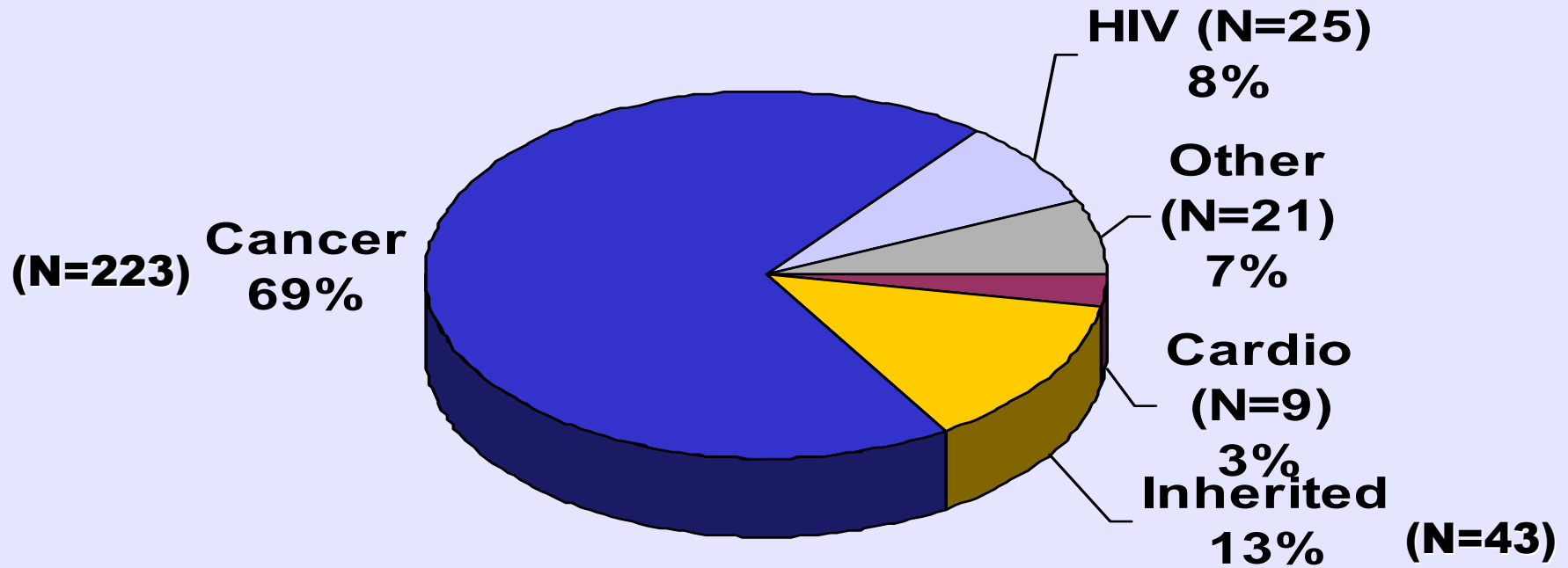
Consent Form Coding & Analysis

- Collect, anonymize, and review all GTR consent forms and protocol summaries or Appendix M responses reviewed by the Recombinant DNA Advisory Committee, 1990-2000 ($N=321^*$ CFs)
- 94-Item assessment instrument, developed, validated, and applied by investigator coding pairs

Consent Form Assessment Topics

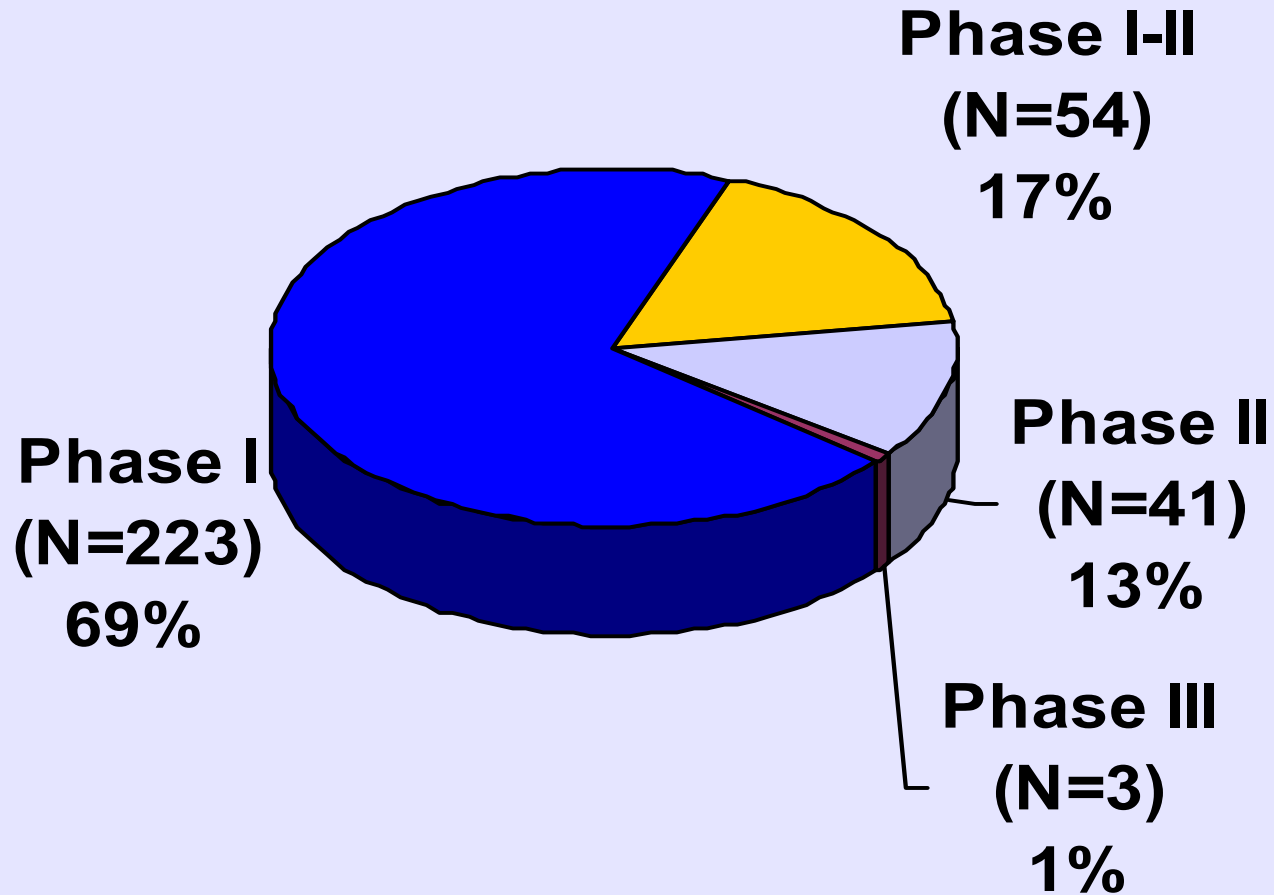
- **General study characteristics** (type of GTR, disease category, study phase/design, vector, delivery system)
- **Pre-clinical or clinical evidence** of direct benefit (or risk)
- **Benefit Discussion:** Type of information provided re *nature, magnitude (size and duration), and likelihood of benefit to subjects*, in 5 sections of the CF, and in protocol summary
- **Language Use:** patient/subject, physician/investigator, research/treatment language for intervention

Disease Type (N=321 Total)



*“Other” includes but is not limited to peripheral vascular disease, arthritis, diabetes, combinations of HIV plus malignancies, etc.

Phase (N=321 Total)



Dose Escalation Described?

Model Dose Escalation Explanation:

We do not know what the highest safe dose of the experimental intervention is, so we will give it to 5-10 subjects at one dose before increasing the dose given to the next group of subjects. The dose you will receive will depend on both the number of subjects who have received the experimental intervention before you and any side effects they had. The investigator will discuss with you where your dose falls and how many subjects have been enrolled, so that you may weigh your potential risks and benefits. Since the intervention is experimental, side effects and benefits at any dose are not yet known.

Minimal Dose Escalation Description:

Three different doses of X will be used in this study. The dose you get depends on when you join the study.

“Empty” Benefits

“Empty” Benefit Statements:

(No nature content; likelihood indeterminate)

- *You may or may not benefit*
- *You may not benefit*
- *Personal benefit cannot be predicted*
- *Personal benefit cannot be promised*
- *Personal benefit cannot be guaranteed*

“Empty” Benefits Sections:

In every GTR consent form having only an “empty” benefits section, more specific benefit information was provided in at least one other CF section (usually the Background/Purpose section).

Does CF Describe Study as Treatment?

Treatment Term in Title:

Example: “B1E7 as Treatment for X Disease”

Treatment Term in Text:

Example: “If you enroll in this treatment program....”

“Treat” as Verb in Text:

Example: “20 patients will be treated on this study.”

Benefit and Study Purpose

- **Purpose of Study**
 - detailed description of ultimate goal of line of research: successful treatment
- **Why Subject is Being Asked to Participate**
 - because nothing else has worked (implication: needs a “new treatment”)
- **Potential Benefit**
 - often characterized by vagueness (examples: may or may not, not possible to predict, cannot be guaranteed; often, endpoints detailed in Purpose and not mentioned in Benefits)
- **Result: *Purpose/Benefit Disconnect***

Two Sites, Same Phase I Study

Purpose Sections

1. “The purpose of this study is to find out if it is safe to give an experimental vaccine to people with your type of brain tumor. We also will attempt to find out if this experimental vaccine can help to increase the ability of your immune system to fight brain tumor cells.”
2. “The purpose of this study is to increase the ability of your immune system to fight your brain tumor cells.”

Two Sites, Same Phase I Study

Benefits Sections

1. **“Are there benefits to taking part in the study?”**

You should not expect to gain any benefit from taking part in this study. We hope the information learned from this study will benefit other patients with a malignant brain tumor in the future.”

2. **“Benefits of Research to Patient:**

While *there is no guarantee* that you will personally benefit from participating in this study, *this research could benefit you* in the following ways: It is possible that this treatment *may start or strengthen your immune system’s ability to fight the cancer in your brain*. However, even if this occurs, *there may still be no beneficial effect on the course of your illness*. However, because of your participation in this study, the investigators may learn more about the role of the body’s immune response against cancer and about the use of tumor cells and immunotherapy. This information may prove useful in the therapy of patients in the future.”

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.

Assessment of Terms in CFs

In a random 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

Terminology Coding Categories

Term Categories	Treatment Terms	Mixed Terms	Neutral Terms	Research Terms
GTR Intervention	Treatment Active treatment Gene-treated cells Therapy New treatment “B1E7” treatment Treatment group Treatment phase	Study treatment Experimental treatment Unproven treatment Gene therapy Vaccine New vaccine Drug New drug	Procedure Infusion Injection Insertion Intervention “B1E7” Product	Gene transfer Study procedure Experimental agent Experimental vaccine Experimental drug/product Investigational drug/product Study drug Experimental “B1E7”
Subject	Patient	Patient-subject Reseach patient	Person Individual Woman Man Human	Subject Study subject Experimental subject Research subject Volunteer Participant
Investigator	Physician Doctor	Study doctor Study physician Physician-investigator	NA	Investigator PI Researcher Study team

Language Matters

We found:

- ALL TYPES OF TERMS were used for the SAME person or intervention in the SAME consent forms
- Many different terms of same type were used for the same person or intervention in the same consent forms
- i.e., no term consistency in ANY CF in sample

GTR Consent Form/Process: Conclusions

GTR consent forms may promote confusion about what to expect from the experimental intervention:

- **Important information described vaguely**
- **Descriptive variety across consent form sections**
- **Some terminology inconsistent/contradictory**
- **Surrogate efficacy endpoints as potential direct benefits:**
 - *Misleading to subjects?*
 - *Applicability in early-phase trials?*

Consent Form/Process: Recommendations

- **Keep consent form/process simple & clear**
- **Tighten use of terminology**
- **Avoid vagueness & inconsistency of language; minimize “elegant variation”**
- **Always present benefit to society as the sole or primary goal of clinical research**
- **Describe study design (especially dose escalation) to help subjects recognize that they are not patients**
- **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

Consent Form/Process

- **Clearer consent form/process may help ALL parties**
 - investigators
 - study coordinators
 - subjects
 - IRBs and other oversight bodies

distinguish *hopes* from *reasonable expectations* about participation in GTR and other early-phase clinical trials