Risks of Harm & Potential Benefits in Research: A Primer

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This Presentation Addresses:

- A typology of risks of harm in research
- A typology of potential benefits in research
- How subjects and investigators think about potential benefits
- How research consent forms describe potential benefits
- Money payments to research subjects
- How IRBs should weigh and balance risks of harm and potential benefits

Risks of Harm: Categories

- **Categories of Possible Harm**
  - Harms from receiving the experimental intervention
    - Often of greatest concern to subjects
    - Often of greatest uncertainty as well
  - “Inclusion harms” from study participation
    - Examples: limitations on personal care; design inflexibility; schedule

Risks of Harm: Types

- **Types of Possible Harm**
  - Physical
  - Psychological/emotional
  - Legal/economic/social
  - Harms to individuals
  - Harms to communities and groups
  - May be certain (burdens) or uncertain (risks)

Risks of Harm: Dimensions

- **Dimensions**
  - ***Nature***
  - ***Magnitude***
    - size
    - duration (temporary? permanent?)
  - ***Likelihood***
    - Some harms are certain
    - Evidence and uncertainty
    - Understanding likelihood

Harms to Groups

- Consideration of possible harms arising from the results of research is explicitly excluded from the IRB's consideration (45 CFR 46.111(a)(2))
- Increasing awareness of possible harms arising from research results
- Need to address these risks of harm
  - In design and initial approval of research
  - In review of results
  - In dissemination of results
- If not IRB, then who?

Benefits: Types & Dimensions I

- **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?

Benefits: Types & Dimensions II

- **“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

Eye of the Beholder

- Some possible outcomes may be either harms or benefits:
  - often true of “inclusion benefits”:
    - additional attention, testing, etc. may be benefit or burden
    - opportunity to talk may help or harm
  - what’s good/bad for a community may not be good/bad for an individual subject
- IRB, PI, CAB discussion/planning needed

Discussing Direct Benefit

- Sources of information and discussion:
  - Media descriptions of research
  - Scientific literature (positive results emphasized)
  - Advertisements soliciting subjects
  - Research consent forms and the consent process
  - Investigators, study coordinators, IRB members, regulatory authorities

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; relief of symptoms; improve quality of life; improve immune system function
- **Clinical endpoints (clearly perceptible)**
  - cure; remission; live longer; improved breathing; fewer infections

Therapeutic Misconception/ Mis-estimation

Many subjects misunderstand and/or are misled about:

- the difference between research and treatment
- the nature, magnitude, and likelihood of potential direct benefit

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"

Informed Consent Project

Social Construction of Benefit in Gene Transfer Research:

http://socialmedicine.med.unc.edu/scob

Interviews: Did Early-Phase GTR Subjects Expect Direct Medical Benefit?

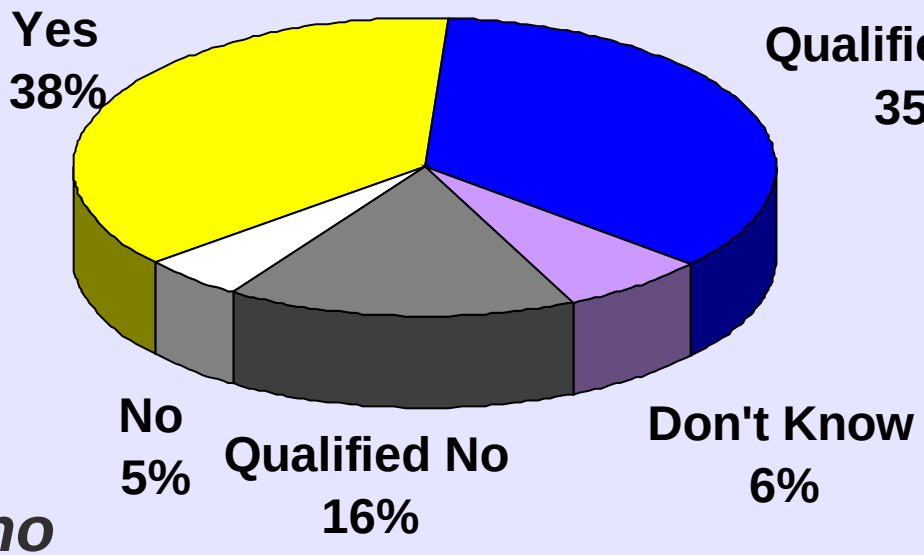
"Did you expect that getting the gene transfer would improve your condition or help make you better? Would you say yes or no?"

75% of subjects answered, **"yes,"** they expected the gene transfer would improve their condition or help make them better.

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."

What Did They 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”

Interviews: What Did PIs Expect?

"Did you expect that the gene transfer intervention in this study would have a direct medical benefit for your subjects?"

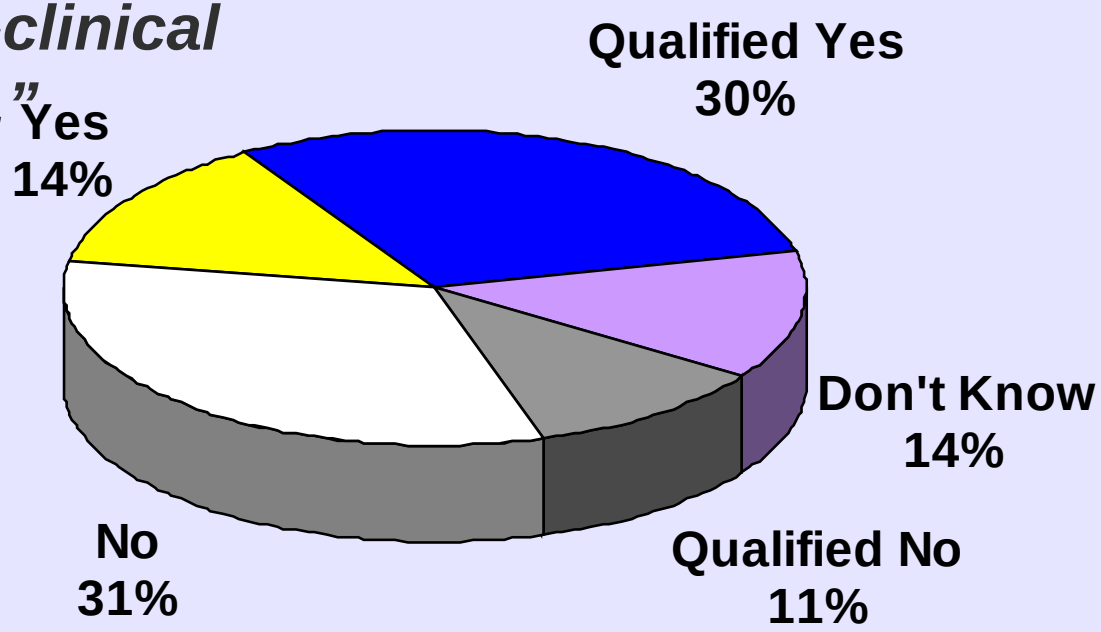
46% of PIs said, "yes"

54% of PIs said "no" or "don't know"

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."

What Did PIs Expect/ Hope For?

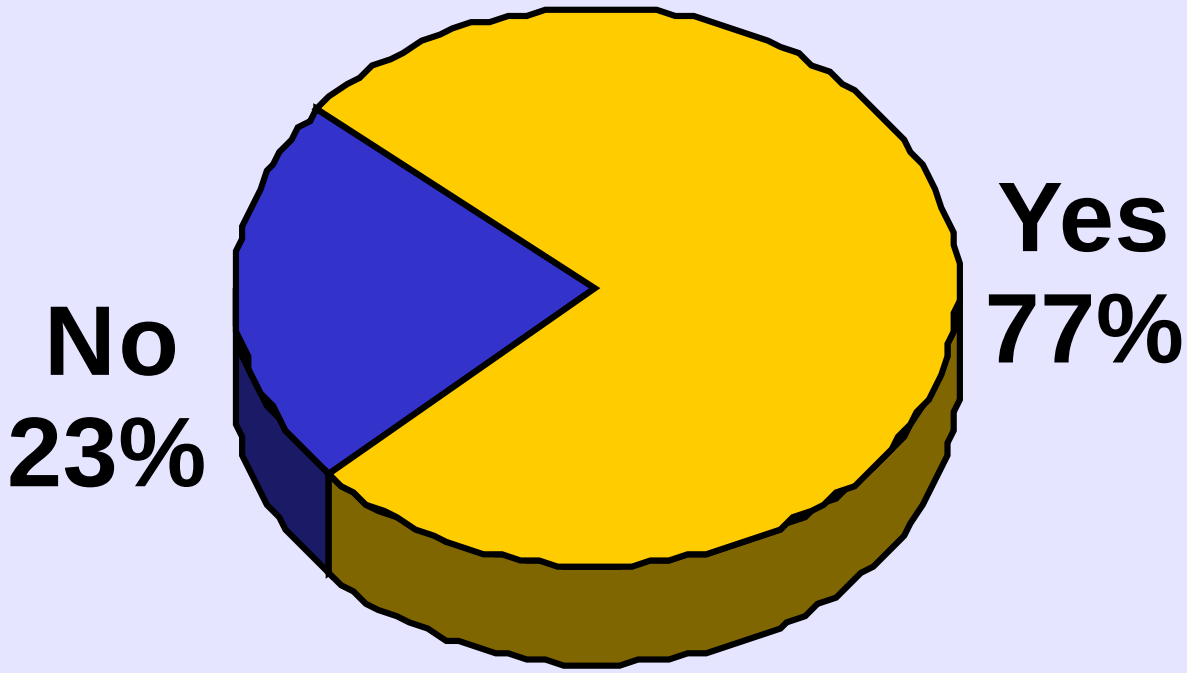
Surrogate Endpoints

- **Tumor shrinkage**
- **Have the vector produce factor**
- **Boost the immune system**
- **Stimulate anti-tumor response**
- **Grow new blood vessels**
- **Keep the tumor localized**

Clinical and Vague Clinical Endpoints

- **Longer survival**
- **Eliminate the pain that they are having**
- **Decrease severity of infections**
- **Restore normal circulation**
- **Avoid amputation**
- **Decrease symptoms**
- **Clinical benefit, positive results, therapeutic option**

Benefit to Society Mentioned?



Does CF Describe Study as Treatment?

Treatment Term in Title: 52 (16%)

Example: "B1E7 as Treatment for X Disease"

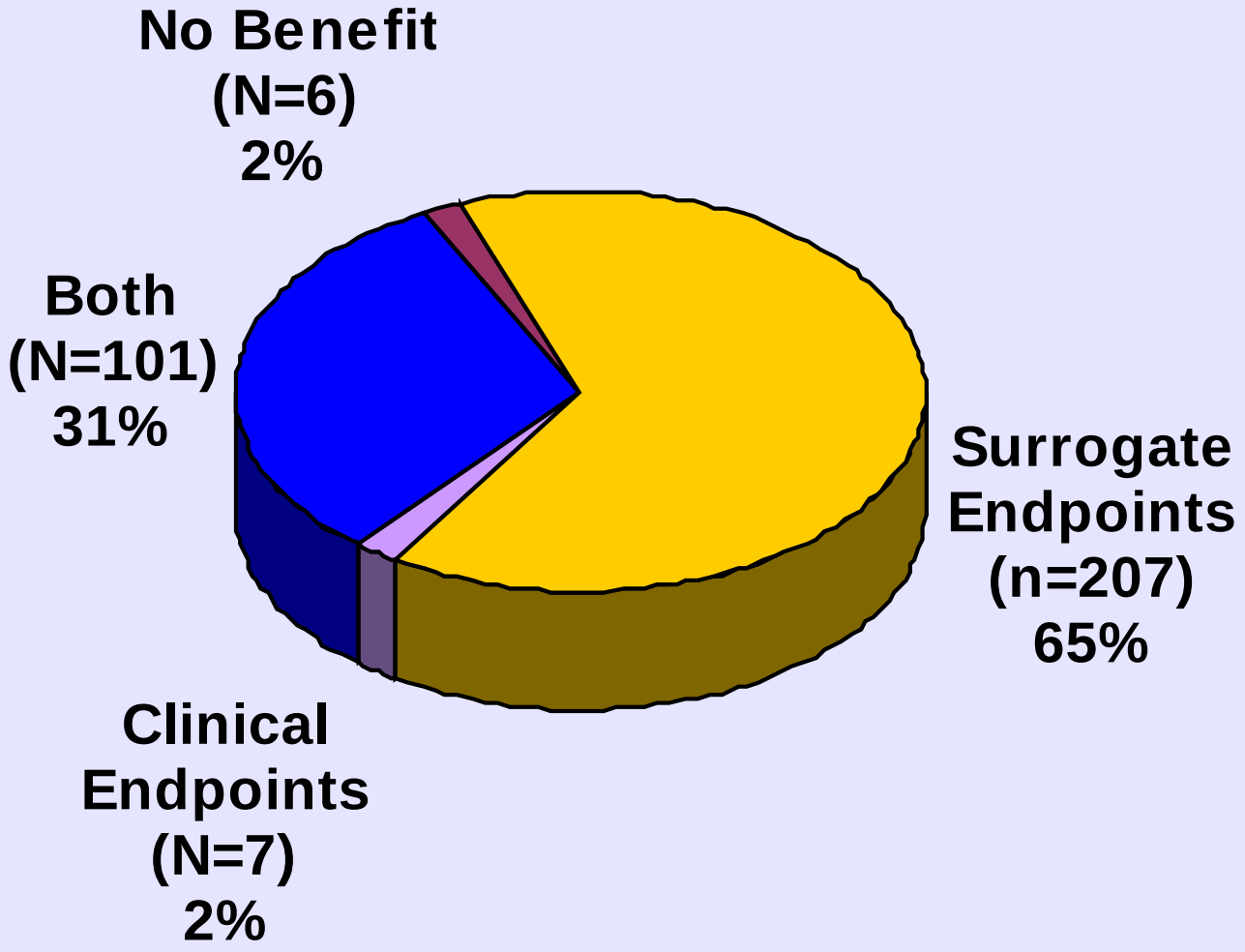
Treatment Term in Text: 46 (14%)

Example: "If you enroll in this treatment program…."

"Treat" as Verb in Text: 125 (39%)

Example: "20 patients will be treated on this study."

Does CF Offer Direct Benefit to Subjects?



How Common are “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*

Be *specific and descriptive* about:

- *potential benefits to subjects*
- *study design*

Don’t oversell direct benefits; be realistic.

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.”

Belmont on Balancing

- Learning *what will in fact benefit* may require exposing subjects to risk.
- [R]isks to subjects [must] be outweighed by the sum of both the anticipated benefit to the subjects, *if any*, and the anticipated benefit to society in the form of knowledge to be gained from the research.
- [B]enefits and risks must be "balanced" and shown to be " in a favorable ratio." The metaphorical character of these terms draws attention to the *difficutly of making precise judgments*…. However, the idea of a *systematic, nonarbitrary analysis of risks and benefits* should be emulated insofar as possible….

Balancing Harms and Benefits

- You can’t buy risks
- But “coercion” is misused/overused
- First, minimize risks of harm
- Then determine if potential harms are “worth” societal benefit (and individual direct benefit *IF ANY*)
- Then design inclusion benefits as *contextually reasonable incentives* (cf. “fair benefits” concept)

Paying Subjects

- Is payment a benefit?
- $ vs. inclusion benefits
- Value is in the eye of the beholder
- You can’t buy risks
- “Coercive offers”?
- Proposing a payment requirement
  - To underscore research-treatment distinction
  - To demonstrate respect for contributions
  - To offset inconveniences of participation

How (Well) Do IRBs Assess and Balance Harms and Benefits?

- IRBs should ask: Is this a fair offer to subjects?
- THEN address subjects' desire to participate
- Context of the condition and its treatment is important: What else is available? How well does it work? etc.
- Assessing uncertainty is singularly difficult
- Assessing investigators' scientific data and claims can stretch IRBs' capabilities and call for consultants
- IRBs often feel inadequate to the task (van Luijin et al., Ann. Oncol.2002;1307-13)
- IRBs should ask for all the information they need
- Making more explicit assessments and comparisons could promote better use of data and help build expertise