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Consent Forms and the Therapeutic Misconception:

The Example of Gene Transfer Research

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Appelbaum and colleagues first described the "therapeutic misconception" in 1982.[1] There has been much discussion since then about whether and why some patients who enter clinical trials confuse research with treatment and overestimate the nature or likelihood of benefit to them from research in which they enroll, and about whether investigators share in or contribute to any misunderstanding.[2] The therapeutic misconception has been examined empirically in surveys and interviews,[3] some of which focus on phase I trials,[4] and in one published examination of consent forms for phase I oncology research.[5] Thus, Appelbaum and colleagues' original focus on whether research subjects understood how study design elements like randomization and placebo arms could affect them has expanded to encompass factors characteristic of early-phase trials, such as translation from laboratory and animal studies to human trials and the implications of dose escalation design. However, there has been relatively little discussion of these and other ethical and design questions raised by early-phase clinical research.[6]

To examine how consent forms for early-phase trials address scientific uncertainty and describe potential benefits, we analyzed 321 consent forms for gene transfer research, 99% of which were early-phase (phase I, I/II, or II) trials, and 69% of which were oncology trials. Our goal was to assess how consent form language might promote or reduce the therapeutic misconception (including misestimation[7] of potential benefit) in early-phase research.

We chose to examine how the prospect of benefit is described in gene transfer research for several reasons. This small but rapidly growing field of clinical research is based on what seems to be compelling scientific logic: since genes direct vital cellular functions, then inadequate cellular functioning should be treatable if new copies of healthy genes are added.[8] Just 15 years old, gene transfer research holds out both great promise and great uncertainty; commands considerable public attention, both positive and negative; and exemplifies the ethical challenges of disclosure in the face of unknowns, uncertainties, and the high failure

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Table 1.
Nature of Direct Benefit in Consent Forms

Nature Category	*Definition*	*Consent Form Examples*
Contentless	no nature information	you may or may not benefit; personal benefit is not guaranteed
Surrogate Endpoint	laboratory measurement that stands in statistically for a clinical endpoint	tumor shrinkage, decrease in PSA, increased % Factor IX in blood, decreased $CD4^+$ count
Clinical Endpoint	specific benefit that can be felt or experienced by subjects	live longer, fewer bleeds, cure, remission, less leg pain, fewer lung infections, improved breathing

potential for early-phase research.[9] Gene transfer research also receives extra guidance and oversight;[10] its consent forms undergo greater scrutiny and must conform to additional standards. This increased attention might be expected to improve the discussion of possible benefits to potential subjects.

Defining Benefits in Clinical Research

To characterize the potential benefits described in early-phase gene transfer research consent forms, we applied the following definitions. Failure to distinguish among the types of benefits in consent forms may both reflect and contribute to conceptual confusion.[11]

First, *benefits to subjects* (benefits from study participation) should be distinguished from *benefits to society* (future benefits to science or to future patients from research results). Because benefits to society—described in federal research regulations as contributions to generalizable knowledge—can only be realized in the future, they should be readily distinguishable from benefits to subjects. However, when consent forms describe the ultimate aim of the line of research or the mechanism of action of the experimental intervention without differentiating these from potential benefits for subjects in the current trial, it may be difficult to distinguish between benefits to subjects and benefits to society. The following example illustrates this blurring: "Gene therapy works by using a virus vector to carry the new gene into the patient's cells. Once there, the new gene makes the protein that patients like you lack. The investigators hope that gene therapy will be an effective treatment for your disease."

Benefits to subjects are further divided into two types: *direct benefits* from receipt of the experimental intervention, and *inclusion benefits* (also called collateral or indirect benefits), which result from participating in a study regardless of whether the subject receives the experimental intervention. The potential direct benefits that may be described in a consent form (Table 1) depend on the nature of the experimental intervention and the subjects' disease or condition. Inclusion benefits need not be so study-specific; descriptions in consent forms can encompass such diverse items as free goods or services provided as an enrollment incentive; diagnostic testing and standard treatments provided on-study at no cost to subjects; the opportunity to be monitored closely by disease experts; and sometimes, potential psychological benefits from "doing everything possible" for oneself and/or for others. Although direct and inclusion benefits are quite different, they are not always distinguished in consent forms. A consent form statement discussing potential benefits to the subject from "study participation" may refer to direct benefits, inclusion benefits, or both, and it may be difficult to determine which type is meant.

Study Methods

We obtained copies of all consent forms and portions of protocols for human gene transfer studies dating from 1990 through August 2000 that are on file and publicly available at the Office of Biotechnology Activities (OBA) of the National Institutes of Health (NIH). All documents were redacted before analysis to delete information that could identify individuals, sponsors, and institutions. Gene transfer studies were excluded from the analysis if their files were confidential, unavailable, or incomplete. Studies using healthy volunteers as subjects were also excluded, as were gene marking studies, which provide data on the feasibility and efficiency of gene transfer using only genes with no therapeutic potential. The resulting total of 321 consent forms represents over 90% of non-marking gene transfer studies submitted to OBA during the first 10 years of human gene transfer research. Institutional Review Boards (IRBs) at the University of North Carolina at Chapel Hill and the National Human Genome Research Institute approved the study.

All consent forms and protocol materials were assessed with a 94-question instrument developed iteratively using practice protocols.[12] Eight investigators working in teams of two coded the materials, with one

Table 2.
Terminology Coding Categories

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

investigator (NK) serving as a member of every team. Each team reconciled disagreements, and Kappa scores were calculated for each item. Kappa scores measure the amount of agreement beyond what would be observed by chance (measured as 0); perfect agreement is measured as 1. All scores for data presented here were in the moderate range (.41 to .60).[13]

■ ***Descriptions of Potential Benefit.*** We looked for descriptions of direct, inclusion, and societal benefits in the five major sections of the consent form: Background/Purpose, Procedures, Risks, Benefits, and Alternatives. We examined each description of potential direct benefit according to the following dimensions: nature, magnitude, duration, and likelihood. We divided descriptions of the *nature* of potential direct benefits into contentless (no description, e.g., "benefit"), surrogate endpoints (measurements substituted for experiences, e.g., "tumor response"), and clinical endpoints (specific and experienceable, e.g., "live longer")[14] (Table 1). We divided statements about the *likelihood* of potential direct benefits into likely, unlikely, and indeterminate (probability statements that could not be further specified, e.g., "may or may not"; "you might"; "cannot be predicted"). We also recorded when no mention was made of benefit in a section, when there was no such section, and when the section said, "You will not benefit."

We coded mentions of surrogate and clinical endpoints *only* when coders agreed that the endpoint was described or offered as a benefit. For example, "your tumors may shrink" and "we will check to see if your tumors shrink" were coded as surrogate endpoints offered as potential direct benefits, whereas "any changes in tumor size during the study will be recorded" was not. Statements like "may help cause remission of your disease" were coded as clinical endpoints offered as direct benefits, whereas statements like "we hope that this research is the first step toward a future cure for this disease" were not.

■ ***Language Use.*** We also collected information about the use of research and treatment terminology in the consent form, such as whether treatment terms were used to describe the entire study, and what terms were used to describe subjects in conspicuous places, such as the study title at the beginning of the consent form or the signature line at the end. In addition, we examined language use in more detail in 20% of the 321 consent forms (N=68). Consent forms were ordered by date and a systematic sample of every fifth consent form was drawn. In this sample, we counted the terms that, from context, clearly referred to subjects, investigators, and experimental gene transfer interventions, and categorized each term used as *research, treatment, mixed* (combining references to research and treatment), or neutral (implying neither research nor treatment). Each of

Table 3.
Characteristics of the 321 Gene Transfer Studies

Characteristics	*Frequency*	*Percentage*
Phase		
I	223	69%
I/II	54	17%
II	41	13%
III	3	1%
Disease Type		
Inherited	43	13%
Cancer	223	69%
HIV	25	8%
Cardio	9	3%
Other*	21	7%
.		
Study Design**		
Dose-Escalation	174	54%
Placebo-Controlled	15	5%
Other Comparison Groups	53	17%
Gene Transfer Alone or in Combination		
GT Alone	212	66%
GT + Standard Tx	22	7%
GT + Standard + IT***	4	1%
GT + IT	74	23%
Other	9	3%

* Other includes but is not limited to peripheral vascular disease, arthritis, diabetes, combinations of HIV plus malignancies, etc.
** Only design features involving study-driven group assignment were coded.
*** IT=investigational treatment.

these categories included multiple terms (Table 2).

Study Results

■ ***General Characteristics of Studies.*** Table 3 summarizes the 321 gene transfer studies. They are almost entirely early-phase. The majority (69%, N=223) were cancer trials, with the remainder distributed among trials for inherited disease, HIV, cardiovascular, and other diseases. Two-thirds of the studies (N=212) examined a gene transfer intervention alone; most of the rest (N=100) also included investigational and/or standard treatments.

Three-quarters of studies assigned subjects to different intervention groups. Most were non-randomized assignments to dosage groups, primarily dose escalation studies (54%, N=174); a few employed randomized designs with placebo or standard treatment comparison arms. Notably, consent forms for 49% (N=85) of the dose escalation studies failed to explain the design to subjects.

■ ***Are Potential Direct Benefits Offered to Subjects?***

• **Nature, Magnitude, Duration of Benefits.** We examined the entire consent form for descriptions of potential direct benefit. Almost all consent forms mentioned the potential for direct benefit to subjects (Table 4). More than half (65%, N=206) described only surrogate endpoints as potential benefits. A third (31%, N=102) described both clinical and surrogate endpoints, and a few described only clinical endpoints. These frequencies did not differ by study phase. Descriptions of surrogate and/or clinical endpoints as potential direct benefits were found more often in Background/Purpose sections (91%, N=293) than in Benefits sections (62%, N=208). Potential direct benefits were less frequently offered in other consent form sections. Consent forms for inherited disease trials were significantly more likely than those for cancer trials to offer both surrogate and clinical endpoints as direct benefits, but also significantly more likely not to offer any benefit (data not shown).

It was common for different sections of the same consent form to convey divergent information about potential direct benefits. For example, in 56 consent forms the Benefits section contained only contentless benefit statements of indeterminate likelihood, such as "You may or may not benefit" or "Personal benefit cannot be guaranteed." However, all 56 provided more specific descriptions of the nature of potential benefit in other sections, as in the following consent form for a phase I trial. The purpose section states in relevant part: "The hope is that we can improve your symptoms and prolong your life with this treatment...The purpose of this study is to determine whether this procedure is safe and to evaluate the effect of this treatment on your disease." The Benefits section states in relevant part: "It is not possible to predict whether or not any personal benefit will result." Although 15 consent forms (less than 5%) said, "you will not benefit" in at least one section, nine of these offered a description of

the nature and likelihood of potential direct benefit in another section of the consent form. Only six consent forms (less than 2%) conveyed consistently that subjects would not benefit from the experimental intervention.

Descriptions of direct benefits rarely included information about potential magnitude or duration (data not shown).

• **Likelihood of Benefits.** Likelihood statements in 83% (N=267) of consent forms were coded as indeterminate. Only 14% (N=45) of consent forms stated that direct benefit to subjects was unlikely. Of these, 44 were for phase I studies. Consent forms for phase I studies were thus significantly more likely to state that direct benefit was unlikely, yet this number still represented only 20% of phase I studies.

• **Inclusion and Societal Benefits.** Nearly a quarter of consent forms (23%, N=73) failed to mention benefit to society. This percentage did not vary by phase. Inclusion benefits were rarely discussed, consistent with IRBs' ambivalence about whether and how to discuss them.[15]

• **Consent Form Language: Research or Treatment?** In 16% of consent forms (N=52), "treatment" and "therapy" were used inappropriately in the title of the study to refer to the experimental gene transfer intervention, e.g., "B1E7 as Treatment for X Disease." The whole study was referred to as a treatment in the text of 14% (N=46) of consent forms (e.g., "If you enroll in this treatment program…."). "Treat" was used as a verb in consent form text in connection with the experimental intervention (e.g., "20 patients will be treated on this study") in 39% of consent forms (N=125). "Patients" was used in the study title to refer to subjects in 49% of consent forms (N=158).

More revealing is our detailed language assessment of a sample of 68 consent forms. In each consent form, we counted all terms used to describe subjects, investigators, and the gene transfer intervention, and categorized each term as *research, neutral, mixed,* or *treatment* (Table 2). We then counted all terms and examined the percentages of terms in each category, thus creating a "language map" of each consent form. Language consistency would be highest if a consent form used terms from one category only; inconsistency would be demonstrated by using terms from multiple categories, especially terms from the most disparate categories, research and treatment.

When referring to the *subject*, all but one consent form in this sample used terms from multiple categories, with "patient" (representing the treatment category) predominating in about half of the forms; 38% (N=26) used terms from only the research and treatment categories (e.g., "subject" and "patient" used interchangeably). The one consistent consent form used only "patient." When referring to *investigators*, almost 30% (N=20) consistently used only research category terms; one consent form used only treatment terminology (e.g., "physician"). The rest combined terms from multiple categories, including 41% (N=28) that used only terms from the research and treatment categories (e.g., "investigator" and "doctor" used interchangeably).

The pattern of language referring to the *gene transfer intervention* showed mixing of terms from different term categories in every consent form, with almost all using terms from all four categories. This language assessment thus demonstrates considerable inconsistency in terminology referring to subjects, investigators, and the gene transfer intervention in every consent form; these patterns of inconsistency did not change over the 10-year time period represented.

Discussion and Recommendations

Some investigators, IRBs, and scholars maintain that the therapeutic misconception is difficult to eradicate, because when subjects are ill and desperate, they will hear and believe what they want to hear and believe about the potential benefits of research for them no matter what they are told. Yet we cannot conclude that what subjects are told doesn't matter unless we know what they are told. What we found in our analysis of 321 gene transfer research consent forms demonstrates that most patients who are subjects have *not* been given clear and unambiguous information about potential benefits—not even in consent forms for early-phase research, where the potential for direct benefit is admittedly low.

Our analysis of consent forms reveals vagueness, inconsistency, and overstatement, all of which may promote confusion about what subjects can expect from receiving the experimental intervention. We found that

Table 4.
Endpoints Offered or Described as Potential Direct Benefit to Subjects*

Endpoint as Benefit	*Frequency*	*Percentage*
Surrogate	206	65%
Both Surrogate and Clinical	102	31%
Clinical	7	2%
No Benefit	6	2%

*Additional vaguely described clinical endpoints (e.g., "symptom improvement") were offered as direct benefits in less than 14% of consent forms, all of which also offered surrogate endpoints. Data not shown.

Table 5.
Recommendations for Consent Forms in Early-Phase Clinical Trials

Avoid Inconsistent and Confusing Terminology:
- Keep terms clear and simple; define them succinctly when necessary
- Describe potential direct benefits* consistently throughout the consent form, or limit their description to one consent form section only
- Limit variation in use of terms referring to the experimental intervention

Avoid Misleading "Treatment" Implications:
- Present benefit to society as the sole or primary goal of the research
- When direct clinical benefit* is not possible or not likely, say so
- Distinguish the ultimate goals of the line of research from what is possible for subjects in the study
- Describe surrogate endpoints* as measurement goals only
- Consistently use "research" terminology to refer to investigators, subjects, and experimental interventions

Avoid Vagueness about Potential Benefits:
- Avoid "empty" benefit statements* like "you may not benefit if you join this study"
- Discuss each type of benefit (societal, direct, and inclusion) separately and distinctly
- When direct benefits are reasonably possible, describe them precisely, including their nature, magnitude, duration, likelihood, and limits
- Clarify whether and how surrogate endpoints relate to potential direct benefits
- Link any potential direct benefits explicitly to receipt of the experimental intervention (not just to "being in the study")
- If describing inclusion benefits,* do so precisely; link them explicitly to participation independent of receipt of the experimental intervention

*For definitions and examples of terms, see text and Table 1.

some key information, such as reference to societal benefit or explanation of a dose escalation design and how it affects subjects, was often not provided. We found considerable divergence, and sometimes inconsistency, in descriptions of the nature of direct benefit offered in different sections of the same consent forms. We found surrogate endpoints often described as potential direct benefits for subjects, even in phase I trials. And we found much terminological variety, including extensive references to the experimental intervention as "treatment," which might contribute to confusion about whether the subject was participating in research or receiving treatment.

Contentless, indeterminate benefit statements like "You may or may not benefit" and "Personal benefit cannot be guaranteed" are in our view too vague to convey meaningful information to subjects. Such "empty" statements are mere truisms, which fail even to distinguish research interventions from standard treatments. More important, we never found them standing alone; either in the same section of the consent form or in another section, all such statements were accompanied by more specific descriptions of surrogate or clinical endpoints offered as potential direct benefits. This makes it even more difficult to imagine what these empty statements were intended to convey, or how subjects might interpret them.

We believe that overstatement and vague or inconsistent language describing potential benefit stems from four problems: 1) simple inattention, by investigators and IRBs, to the language used in the consent form as a whole;[17] 2) collective lack of experience and guidance in describing potential benefits (as compared with risks of harm);[18] 3) differences of viewpoint and lack of consensus among investigators,[19] IRBs,[20] and scholars[21] about how best to describe potential direct benefits to promote subjects' understanding, especially in light of the complexity and uncertainty of early-phase research; and 4) consent form authors' and reviewers' own therapeutic misconceptions about the research enterprise in general and the purpose and promise of particular research.[22]

We have listed our recommendations for addressing these problems in Table 5.[23] The first two problems can be easily corrected. It should not be difficult to improve the clarity and consistency of terms referring to subjects, investigators, and experimental interventions. Similarly, it is possible to avoid inconsistency and contradiction in descriptions of potential direct benefit across different consent form sections, especially when care is taken to distinguish the goals of the line of research, described early in the consent form, from the potential direct benefits to subjects described later. And all consent forms can be required to mention—and highlight as the study's principal goal—benefit to society, and differentiate that from direct benefit to subjects.

Nonetheless, the third and fourth problems we have noted will not be so easily remedied, because they reflect unresolved debates about the goals of clinical research and the moral duties of clinical researchers

as compared with the moral duties of health care providers who treat patients.[24] The offer of a clinical endpoint in an early-phase trial almost always substantially overstates the likelihood of direct benefit. Surely few would disagree that such an offer is inappropriate except in rare circumstances and with strong evidentiary justifications. Yet we found many such offers in early-phase gene transfer consent forms. There appears to be more disagreement, however, about whether and how to discuss surrogate endpoints with subjects. We found that surrogate endpoints frequently were not only described as measurement goals for a given study, but were also described as potential direct benefits. Offers of surrogate endpoints as direct benefits are inherently problematic in clinical trials, because they transform into a "benefit" a statistical measure that was never so intended.[25]

Surrogate endpoints are rarely achieved in early-phase studies (the best-known example being a tumor response rate of 5-8% in phase I oncology trials).[26] Thus, even to say "your tumors may shrink" in the consent form may be an overstatement. The greater problem is that, for many reasons, surrogate endpoints often have no clear or direct correlation with clinical endpoints that have value for patients who are subjects and can actually be experienced by them, such as improvement in particular symptoms or reduction in mortality.[27] Care must be taken to avoid the impression that surrogate endpoints are benefits, especially in early-phase trials. This usually means being more specific about what benefits can—and cannot—be reasonably expected for subjects. Thus, a statement like the following is likely to be more accurate in an early-phase trial: "There is a very small chance that your tumors will shrink temporarily, but even if that happens there will almost certainly be no change in the course of your disease or in the length of time you live."

We believe that increased specificity about potential benefits, and the limits thereof, is needed in consent forms for gene transfer and other early-phase research, to ensure that they neither reflect nor contribute to overestimation of direct benefit. However, some investigators and IRBs may prefer less specificity, believing that subjects' hopes are less likely to be raised if less is said.[28] Others may believe that more optimistic presentations of what might happen in a study is justified because gene transfer, like other novel research, would not be pursued if it were not so needed and so promising: "We wouldn't be doing this if we didn't think it would work."[29] Yet the history of clinical trials shows that enthusiasm about new research is not a reliable indicator of the potential for direct benefit.[30]

These differences of viewpoint make it essential to craft better descriptions of potential direct benefits for subjects, including *limitations on what can be expected*. This task is challenging but far from impossible. We urge drafters and reviewers of consent forms to attempt more thorough explications, employing more specific language about the nature, magnitude, duration, and likelihood of direct benefit, to help eliminate inadvertent implications of success and temper potential subjects' willingness to infer it.

The goal of our recommendations is not to squelch the hopes of subjects or investigators. We want only to help all who write, review, and read consent forms to distinguish between *hopes* and *reasonable expectations*, in gene transfer research and other early-phase clinical trials. Despite years of tinkering with consent form language, we are far from accomplishing this critical goal.

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21. See ref. 2, King 2000; ref. 6, Agrawal and Emanuel 2003.

22. See ref. 2, Appelbaum 2002, Dresser 2002.

23. Investigators and IRBs may also consult the web-based informed consent guidance document developed by the NIH Recombinant DNA Advisory Committee. One of the authors (NK) co-chaired the working group that produced this resource. It focuses on gene transfer research but contains more broadly applicable information and sample language, especially for early-phase trials. NIH OBA. *NIH guidance on informed consent for gene transfer research*. 2004 http://www4.od.nih.gov/oba/rac/ic, last accessed July 12, 2004.

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