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Elements of Style: Consent Form Language and the Therapeutic Misconception in Phase 1 Gene Transfer Trials

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ABSTRACT

The therapeutic misconception arises wherever human subjects misinterpret the primary purpose of a clinical trial as therapeutic. Such misconceptions are particularly prevalent in trials involving severely ill subjects or novel and well-publicized investigational agents. In order to identify possible sources of the therapeutic misconception in gene transfer trials, 286 phase 1 human gene transfer consent documents were analyzed for their description of purpose, alternatives, and their use of the term gene transfer. We report that 20% of trials fail to explain their purpose as safety and dosage, only 41% of oncology trials identify comfort care as an alternative to participation, and that the term gene therapy is used with twice the frequency of the term gene transfer. Trends and coherence in consent form language were analyzed as well. Our results indicate that consent forms used in gene transfer phase 1 trials often contain language that promotes, or does little to deter, therapeutic misconceptions.

INTRODUCTION

Clinical trials lodge ambiguously between scientific research and clinical care. On the one hand, drugs with known toxicities or unknown properties are often first tested in participant-subjects who have exhausted standard treatments, partly because of the remote possibility of medical benefit. On the other hand, the primary objectives of clinical trials are scientific, and as such, practices like randomization and rigid dosing regimens interfere with physicians' exclusive commitments to their patients (Schafer, 1982; Appelbaum *et al*., 1987).

Although the main beneficiaries of clinical trials are society and future patients, severely ill subjects generally participate in research for the prospect of treatment, and are therefore prone to misinterpreting trials as aimed primarily at therapy. Such misattribution of therapeutic intent, known as the therapeutic misconception, distorts the consent process by causing subjects to overestimate a study's benefits, underestimate its risks, or overlook noncurative options that offer greater probability of clinical improvement (Levine, 1993; Lidz and Appelbaum, 2002).

Therapeutic misconceptions, which are well documented for oncology trials (reviewed in Lidz and Appelbaum [2002]), may be particularly prevalent in trials of novel biotechnologies such as gene transfer, recombinant drugs, or stem cells. First, these trials often involve greater uncertainty and hazard, and therefore enroll persons with advanced disease who are more susceptible to therapeutic misconceptions (Schaeffer *et al*., 1996). Second, biotechnologies are often regarded by clinicians and the public as heralding revolutionary advances. Third, clinicians who develop novel therapies often conduct their own trials. Their emotional (if not financial) investment in the success of their trials can cause investigator-developers to project therapeutic optimism subconsciously.

In order to examine possible factors influencing therapeutic misconceptions in trials of novel agents, we previously analyzed the description of benefits in human gene transfer (HGT) consent documents used from 1990 to 2001 (Kimmelman and Palmour, 2005). We report here on several other variables that relate to therapeutic misconceptions and informed consent documents, including descriptions of a trial's purpose and alternatives.

MATERIALS AND METHODS

All available phase 1 consent documents for HGT protocols from 1990 to 2001 were collected from the National Institutes of Health's Office of Biotechnology Activities (NIH-OBA). After phase 1/2 trials were excluded, 286 were available. Unlike our previous study, the present one included trials that targeted tissues unrelated to underlying pathology (most of these involved cystic fibrosis studies).

Documents were analyzed using content analysis, which involves the quantitative analysis of written text (Neuendorf, 2002). In this study, only introductory, purpose, benefits, and alternatives sections were analyzed (as described below), be-

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cause we observed during piloting that these sections were the most likely to contain the information we were seeking. Briefly, the occurrence of textual features was scored nominally using variables described in Table 1. Descriptions of trial purpose were identified on the basis of preamble phrases such as, "The goal of this study is . . . " or "This study is being performed to . . . ," and categorized as describing a trial's purpose as testing safety and/or dosage, efficacy, and/or treatment. Any time a document identified efficacy testing as a goal, the sentence was also coded according to whether subjective (e.g., first or second person) or objective (e.g., third person) pronouns or nouns were used for the research subject.

Use of the term "gene transfer" or "gene therapy" within opening and benefit sections was scored as well. Statements that trial participants were unlikely to benefit medically were scored when they appeared in the introduction and benefits paragraphs. Among consent forms used in oncology trials (71% of all forms), descriptions of alternatives to trial participation were analyzed for whether comfort and/or noncurative options were described.

Two coders (the authors) conducted the content analysis with greater than 25% overlapping coverage by each coder for each variable. Intercoder reliability values all exceeded 0.85 as calculated using Cohen's κ. Differences in coding were resolved by discussion and consensus. For forms stating that experimental agents were being administered with therapeutic intent, our intercoder reliability as measured by Cohen's κ was unacceptably low, indicating a high level of subjectivity in interpreting these statements. We therefore submitted all sentences containing possibly inappropriate statements to three ethicist reviewers who have extensive experience participating on Institutional Review Boards (IRBs). Reviewers were instructed to apply stringent criteria in deciding whether statements were inappropriate by giving investigators the benefit of the doubt where statements were ambiguous.

Statistical tests were performed using Microsoft Excel v.X (Microsoft Corporation, Redmond, WA) and Statview 5.0 (SAS Institute Inc, Cary, NC). Significance in χ^2 tests (all of which involved fourfold tables) and linear regressions was defined as $p < 0.05$.

RESULTS

Data from our content analysis are presented in Table 2. To determine which term of art is preferred, we examined whether forms used the term gene transfer. Although the term is often used interchangeably with gene therapy, many ethicists contend that gene transfer more aptly conveys the nonvalidated status of HGT and the scientific orientation of HGT trials (Churchill *et al*., 1998; Juengst and Walters, 1999). We found that a greater proportion of forms used gene therapy than gene transfer. When proportions were calculated based only on those forms that use either term, we found that 79% used gene therapy while 37% used gene transfer (proportions do not add to 100% because some forms used both). We noted a slight but statistically insignificant trend toward the use of the term gene transfer (Fig. 1).

Consent documents generally described phase 1 trials as safety and dosage studies, though as many as one fifth did not. A plot over time (Fig. 1) showed that phase 1 consent documents are improving in this category (Pearson's r value was 0.713; linear regressions showed statistically significant correlation). The use of second-person pronouns within statements saying that a trial's purpose was to determine efficacy was common. We also found 28 instances (10% of forms) in which a majority of our reviewers believed that consent documents contained sentences implying that the trial or the administration of an experimental agent was aimed at providing medical treatment. In 16 instances (5.7%), our reviewers were unanimous in believing the sentences were inappropriate or misleading. Because these sentences are highly problematic from an ethical standpoint, we present examples in Table 3.

When we examined descriptions of alternatives to participation, a majority of oncology trial consent documents identified noncurative alternatives to participation. However, only a minority specifically identified pain, palliation, or supportive care

Table 1. Coding Methodology for Analysis of HGT Consent Documents

Compositional feature	*Section coded*	*Categories*	*Examples*
Gene "Therapy" vs. "Transfer"	T, I, P, B	yes or no	use of term "gene therapy" or "gene transfer"
Description of Purpose	I, P	safety/dose	"the goal of this study is to study the *side effects* . . . " "we are trying to determine a *safe dose* for . . . "
		efficacy	"the purpose of this study is *to see if we can shrink* your tumor"
Subjective Language in Purpose	efficacy purpose statements	yes	"the purpose of this study is to see if we can shrink *your* tumor"
		no	"the purpose of this study is to see if we can shrink tumors in *patients* . . . "
Benefits Unlikely Stated	I, P, B	yes or no	"you are unlikely to benefit from the drug," "this treatment is not a cure," "we do not expect this drug will help you," etc.
Alternative Treatment Goals	I, A	comfort care	palliation, treatment of symptoms or pain, supportive care
		non-curative	Comfort care + option of no further treatment

Section abbreviations: A, alternatives; B, benefits; I, introduction; P, purpose; T, title.

TABLE 2. CODING RESULTS OF HGT CONSENT FORMS

Compositional feature	*Categories*	*Number*	*Percent*
Gene "Therapy" vs. "Transfer"	gene therapy	142	50.2
	gene transfer	66	23.3
Statement of Therapeutic Intent	unanimous	16	5.70
	majority	28	10.0
Purpose Stated as Safety/Dosage	yes	222	79.6
	no	57	20.4
Subjective Language for Purpose: Efficacy	yes	79	43.6
	no	102	56.4
Benefits Unlikely Stated	Intro sec	40	14.1
	Benefits paragr	66	27.6*
	Intro & Ben paragr	20	8.40*
Alternative Treatment Goals†	Comfort care	81	41.2
	Non-curative	140	71.4

* = proportion calculated on the basis of forms containing benefits paragraphs ($n = 240$); † = proportion calculated only on the basis of HGT oncology forms ($n = 196$).

as alternative therapies. We found no significant trends in descriptions of alternatives (Fig. 1).

Table 2 also presents additional data from our previous study. We previously reported that a minority of consent documents state in their description of benefits that direct medical benefit is unlikely, but that some forms make this statement within their introduction. We report here a breakdown of where and how frequently consent documents state that benefits are unlikely. Specifically, a tenth of all forms make emphatic attempts to warn subjects that benefits are unlikely by stating this twice.

We previously identified several compositional practices in consent documents that, we argued, discourage therapeutic misconceptions. These included the mention, within benefits sections, of the possibility of aspirational benefit, the possibility of harm, and the trial's purpose (which is scientific). Another practice was the statement, anywhere in the form, that medical benefits were unlikely. The present study looked at two additional variables that are indicative of caution in consent language: statements of the trial's purpose as safety and dosage, and the use of the term gene transfer.

If the measure of each of these compositional practices were providing an indication of an investigator's attempt to prevent subjects from overestimating a study's direct medical benefits, one would predict that those forms that make use of one cau-

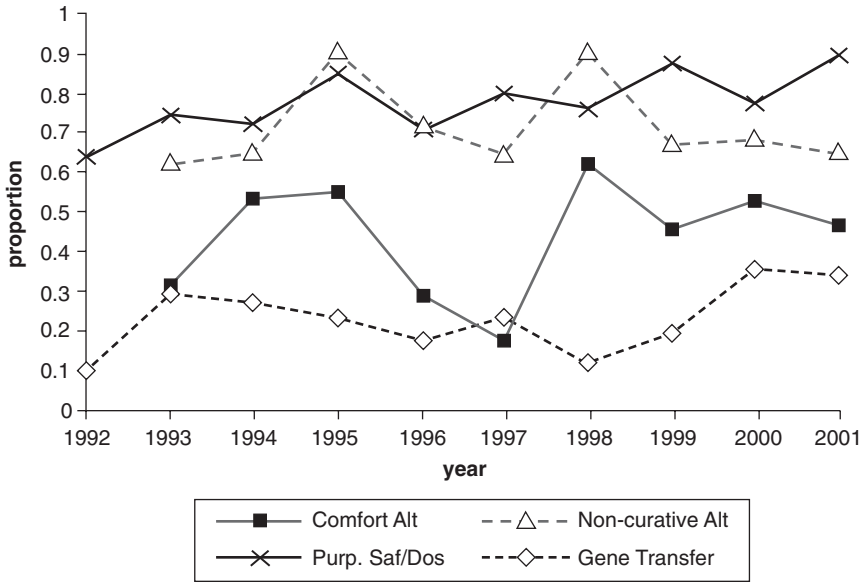

FIG. 1. Trends in consent document language. Proportion of consent forms stating various alternatives, that the trial was aimed at testing safety and/or dosage, and using the term "gene transfer" were plotted over time. Data on alternatives (which were derived only from oncology forms) for 1992 were not plotted because fewer than ten oncology trials were available for coding.

TABLE 3. SENTENCES SUGGESTING THERAPEUTIC INTENT*

- "In this study, a team of physicians and scientists will treat your [disease] by delivering a pair of genes to your [organ]."
- "We would like you to be in a research study of a treatment designed to make your immune system fight the cancer."
- "This study is designed to treat cancer patients with immunotherapy using an experimental anti-tumor vaccine . . . "
- "This is a research study which involves . . . gene therapy in the treatment of patients with [cancer]. The doctors will try to change the nature of the . . . tumor cells . . . by adding a normal gene . . . "
- "The purpose of this study is to increase the ability of your immune system to fight your [cancer]."
- "I am being asked to take part in a research study for the treatment of cancer."
- "The intention of this protocol is to create an immune response to the cancer cells in your body."
- "We would like to treat the disease by helping your body fight it."
- "A gene . . . has been removed from the virus to use in treating your cancer."
- "Our plan is to correct [the disease] by adding a good gene to your [organ] . . . "

*All references to a specific disease or gene transfer agents have been removed to preserve the anonymity of investigators who used these sentences.

tionary compositional device would also make use of others as well. To examine whether forms showed coherence with respect to these measures, we tested whether variables correlated positively with each other. Figure 2 indicates some degree of correlation—and hence consistency—among the variables we used in our content analysis. A p value of 0.05 would predict that 1 in 20 variables would show significant correlation if the relationship among these variables were purely random; we found that, of the 15 tests, three showed a significant positive relationship. Several nonsignificant positive relationships were observed as well, while the only negative correlations we observed had meaningless p values. These correlations are hardly powerful, and we note that many forms harbored contradictory terminology and statements. Nevertheless, we conclude that consent forms show a degree of coherence with respect to language that discourages subjects from overestimating a trial's direct benefits.

DISCUSSION

We previously found, and reiterate here, that consent documents often blur the distinctions between patient care and clinical research in their use of language. As noted by others, they often use terminology more suited to the former (Churchill *et al*., 1998; King *et al*., 2005). This matters, because consent is highly sensitive to linguistic factors (Kent, 1996), and terminology influences how prospective subjects assess a trial's desirability (Sugarman *et al*., 1998) or misunderstand its procedures (Snowdon *et al*., 1997).

Terminology and consent documents

Terminological errors in consent forms fall into three major categories: the use of "physician" for more appropriate terms such as "investigator," the use of the word "patient" to describe the subject (King, 1999), and the use of "therapy" to describe the experimental agent. We studied a variation on the third: references to experimental agents as gene therapy (which suggests therapeutic intent and, from the vantage of the naïve subject, validation) versus gene transfer.

The use of terminologies that suggest therapeutic efficacy is closely related to a tendency in many consent forms to overstate the status of HGT development. Despite a series of publicized setbacks, including a critical report accusing the field of "overzealous representation" of its accomplishments (Orkin and Motulsky, 1995), subjects continue to overestimate HGT's state of development. For example, the father of a subject who died in 1999 after a reaction to an HGT agent testified that he and his son had understood that OTC gene transfer had already shown efficacy when, in fact, it had not (Gelsinger, 2000). While we do not conjecture here on the origins of the Gelsingers' misunderstanding, we note in passing that the consent form used in that trial described the investigational agent as, "a newly developed type of treatment." This statement, while perhaps logical from the perspective of an investigator who has invested years in preclinical development, is possibly misleading to subjects who encounter an agent for the first time in a medical setting. Novel therapeutics like HGT require multiple trials to refine formulations and methods, and are therefore still under development during clinical trials (Antman *et al*., 2001). Especially in the con-

Safety/Dose	G. Transfer	Benefits Unlikely	Harm Possible	Purpose Restated	Aspirat'l Benefit	
	.27	.32	1.0	.69*	**<.001**	Safety/Dose
		.11	1.0	.45	1.0	G.Transfer
			1.0	**.0022**	**.04**	Benefits Unlikely
				1.0	.63*	Harm Possible
					.17	Purpose Restated
						Aspirat'l Benefit

FIG. 2. Correlation of cautionary language among coded variables. Variables were tested against each other using chi-square to determine whether the use of one cautionary language practice correlated positively with the use of others. *P* values are provided. *Denotes that variables were inversely correlated; significant positive correlations are in boldface.

text of early trials of novel approaches such as HGT, consent documents should describe trial agents as still under development rather than as newly developed. Some consent documents appropriately capture the instabilities and uncertainties associated with novel agents when they state, "This is clearly pioneering research, and we have no evidence that this will help you."

Descriptions of a study's purpose

We also believe that consent forms often lead prospective subjects to therapeutic misconceptions in their statement of purpose. Under U.S. federal regulations, phase 1 trials are "Designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness" (21 CFR § 312.21). Nevertheless, many forms fail to state safety and dosage as aims (though there appears to be improvement over the time period studied); moreover, the inclusion of sentences such as those reported here that proclaim or could easily be interpreted as announcing therapeutic intent is clearly inappropriate within phase 1 consent documents.

Another feature of consent documents that can aggravate misunderstandings about a trial's purpose, noted qualitatively here, is entangled descriptions of the purpose, study agent, and benefits. The following example is fairly typical of sentences encountered in the introductions of HGT consent forms: "We would like your child to be in a research study to determine the safety of special cells that may make you/your child's own immune system fight the leukemia." By describing a potential benefit within a sentence declaring the study's purpose, such sentences are easily interpreted as saying that a trial's purpose is therapeutic. Nancy King provides another example that merges a statement of the study's purpose with a description of a study agent's mechanism, "The purpose of this research is to develop a new kind of cancer treatment which works by helping the body's immune system to attack cancer cells." In addition to wrongly implying efficacy in the use of the word "works" (King, 2000), the mechanistic information provided here, intended to enlighten readers about the function of vaccines, can be misinterpreted as describing a benefit of participation. Comprehension of consent forms can be increased by partitioning and organizing descriptions of purpose, agent, and possible benefits (Murphy *et al*., 1999; Bjørn *et al*., 1999). Similar organizational measures may also help prevent therapeutic misconceptions.

Consent form purpose statements can also be confusing when second-person pronouns are used within statements describing a trial's aim as testing efficacy. While the second person enhances readability by making information seem relevant to a reader, it can also inadvertently convey that an action, protocol, or agent is personalized and therapeutic rather than generalized and scientific. Problematic use of second-person pronouns in consent documents arises in two contexts: within descriptions of a trial's purpose (especially when efficacy is being tested) and a trial agent's scientific basis. For example, the statement, "Drug X is being tested to see whether it will induce remission in your cancer" needlessly suggests that the trial is aimed at testing an individual's response rather than the response of a category (persons with a type of cancer). Similarly, the sentence, "Drug Y is designed to stimulate your immune system to kill cancer cells" can easily be read as suggesting that the investigators have a vaccine that is customized for the prospective subject and is being administered primarily for therapeutic reasons. Misunderstandings can be avoided in descriptions of purpose and agents by substituting second person pronoun objects with general categories like "subjects" or, if a second person pronoun is strongly preferred by the consent form's author, "persons with your disease."

Paragraphs describing study benefits are a logical place where therapeutic misconceptions can be abetted or thwarted. The benefit severely ill subjects are most likely to receive from early phase trials—apart from the psychological benefits of preserving hope—is the knowledge that their dying has meaning, and that their participation may benefit others. Regardless of whether phase 1 trials are undertaken with some degree of therapeutic intent, there is little evidence to suggest that enrolled subjects generally benefit; one recent analysis reported a 3.8% objective response rate (Roberts *et al*., 2004). Although subordinate to the desire for personal benefit, persons enrolling in oncology (Daugherty *et al*., 1995; Madsen *et al*., 2002) or treatment (Cassileth *et al*., 1982; Sugarman *et al*., 1998) trials often express altruistic motivations for participation, and subjects who are otherwise disappointed in the medical outcome of a clinical trial often salvage comfort from knowing that they helped to advance medicine (Cox and Avis, 1996).

Many patients with severe illnesses enter early phase clinical trials expecting direct medical benefits (Yoder *et al*., 1997), and their expectations generally exceed those of the clinical-investigator (Cheng *et al*., 2000). While physician–investigators may have humane intentions for not disclosing to subjects the medical futility of their enrollment, such nondisclosure is potentially harmful, exploitative, and threatens the integrity of the medical research enterprise (Annas, 1994). We therefore were interested to determine the proportion of consent documents explaining that medical benefits are improbable, and for those that do explain this, how often the statement is made twice. We found that few forms are emphatic about the low probability of medical benefit. We believe consent forms can navigate the delicate challenge of being truthful without quashing subjects' optimism by stating outright that investigators anticipate indirect or emotional but not direct medical benefits for subjects who participate in trials (Churchill *et al*., 1998).

Description of alternatives

By raising unrealistic hopes for cure, therapeutic misconceptions can cause terminally ill subjects to overlook and postpone noncurative treatment objectives such as palliation that are lower risk and have greater likelihood of achieving success. While sheltering the terminal patient's sense of hope, postponement can also feed denial processes that interfere with a dying person's need to arrange their affairs and achieve closure (Quill, 2000; Block, 2001). In addition, recognition of a terminal prognosis often leads to earlier administration of and greater satisfaction with palliative care (Wolfe *et al*., 2000). We believe that discussion of alternatives in consent documents suffers two major shortcomings. First, our analysis shows that consent documents frequently do not disclose noncurative alternatives such as palliation, supportive care, or treatment of symptoms. Unfortunately, we did not observe significant trends toward improvement in disclosing options like palliation. Second, we observed qualitatively that consent documents often enumerate alternatives in list fashion as if the prospective sub-

ject were choosing among more or less equivalent options. As such, consent forms fail to engage the patient in considering the values and implications associated with choosing among the alternatives. Supportive care, standard treatments, and alternative experimental protocols not only involve different packages of risks, but also distinct objectives (e.g., comfort, cure, and knowledge acquisition, respectively). Consent forms and the discussions they are designed to instigate would be better served if they articulated the objectives associated with alternatives, and the likelihood that such objectives would be attained.

Coherence and validity

Finally, we have used several variables to measure the extent to which consent documents attempt to thwart therapeutic misconceptions. If, indeed, our many variables are measuring linguistic sensitivity on the part of investigators, one would predict that the different variables would have a tendency to appear together with each other in consent documents. With the notable exception of warning that harm is possible within benefits sections, these variables show a tendency to correlate positively with each other, with several associations showing statistical significance. This provides some evidence that our variables are, indeed, successfully measuring therapeutic caution and/or that forms show a degree of consistency in their use of language.

Concluding thoughts

Our findings, while indicating numerous weaknesses in HGT phase 1 consent documents, should be regarded with several provisos. First, we do not claim to have measured the overall quality of HGT consent documents. This analysis, for example, hardly exhausts the various ways that consent documents can influence the therapeutic expectations of subjects; as reported previously, consent documents generally are very diligent about describing uncertainties surrounding direct medical benefit (Kimmelman and Palmour, 2005). Second, we are not suggesting that investigators are intentionally deceiving subjects when they use ethically problematic language, or even that therapeutic misconceptions originate in consent documents. Third, we do not claim to have provided any evidence that the compositional practices analyzed here actually influence subjects' therapeutic expectations. Thus, our argument that terms such as gene therapy or the use of second person within statements that a trial is designed to collect information on efficacy rest on logical inference rather than survey data. Fourth, consent documents are only one aspect of the consent process, and our analysis of consent documents provides limited information about what is said during the informed consent process, and how these communications are conducted. Fifth, objectors could reasonably argue that some of our recommendations are picayune or irrelevant; indeed, consent forms may not significantly influence a person's decision to enroll in medical research (Bosk, 2002), and subject comprehension of consent information has proven resistant to modifications of the consent process (Agre *et al*., 2003; Flory and Emanuel, 2004).

We nevertheless believe that consent document language merits attention from principal investigators and IRBs for several reasons. First, notwithstanding these concerns, consent documents can enhance a subject's understanding of a trial (Riecken and Ravich, 1982), and various interventions in consent documents have, in experimental contexts at least, improved subject comprehension (Flory and Emanuel, 2004). Second, clear and accurate document language displays the good faith of principal investigators to achieve informed consent by respecting the need for subjects to understand a trial. Last and perhaps most importantly, consent forms may offer a useful window into how investigators approach prospective subjects. There is some support for the inference that what is said during the consent process resembles what is presented in consent documents (Henderson *et al*., 2004).

Our results are consistent with those recently reported for 1999 oncology consent documents (Horng *et al*., 2002) and another set of studies examining gene transfer consent documents (Henderson *et al*., 2004; King *et al*., 2005). The oncology study found that forms used in trials of less conventional agents (e.g., biologics and vaccines) were significantly less likely to discuss noncurative alternatives to participation than were forms used in classic chemotherapy trials. While not statistically significant, these data also suggested that consent documents used in trials of less conventional agents were somewhat less likely than classic chemotherapy consent documents to distinguish research from clinical care procedures. These findings, therefore, hint—but do not prove—that consent documents used in nonconventional oncology trials tend to make fewer attempts at thwarting therapeutic misconceptions. The gene transfer consent document studies show widespread use of problematic terminology, and a similarly low frequency with which these consent documents stated that direct medical benefits were unlikely.

We believe that investigators conducting trials using unproven modalities such as HGT can meet their research objectives while counteracting the unwarranted expectations that research subjects often bring to novel therapies like HGT. The therapeutic misconception arises from many sources, and improvement of consent documents is unlikely to eradicate it. Nevertheless, by attending to the language used in consent forms, principal investigators and IRBs can help forestall some of the expectations and misinterpretations that potentially undermine consent in phase 1 trials of novel therapies.

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