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“It is not guaranteed that you will benefit”: True but misleading?

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Abstract

Background—Participants of early phase intervention trials for serious conditions provide high estimates of likelihood of benefit, even when informed consent forms do not promise such benefits. However, some technically correct, negatively stated benefits statements—such as “it is not guaranteed that you will benefit”—could play a role in raising expectations of benefit because in ordinary English usage such statements denote a likely but not a certain-to-occur event.

Methods—An experimental online survey of 584 English-speaking adults recruited online. They were randomized to receive one of two benefits statements (‘not guaranteed’ vs ‘some but very small chance’), using a hypothetical scenario of an early phase clinical trial testing an intervention to treat amyotrophic lateral sclerosis (ALS). We assessed respondents’ willingness to consider participating in the ALS trial, their estimates of likelihood of benefit and their explanations for those estimates.

Results—The two arms did not differ in willingness to consider participation in the ALS trial. Those receiving ‘not guaranteed’ benefit statement had higher estimates of benefit than those receiving ‘some but very small chance’ statement [35.7% (SD 20.2) vs. 28.3% (SD 22.0), $p < 0.0001$]. 43% of all respondents chose expressions of positive sentiment (hope and need to stay positive) as explanations of their estimates; these respondents’ estimates of benefit were higher than others but similar between the two arms. The effect of benefit statements was greatest among those who chose “Those are just the facts” as the explanation for their estimate [31.0% (SD 22.4) in ‘not guaranteed’ arm vs 18.9% (SD 21.0) in comparison arm, $p = 0.008$].

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Conclusion—The use of ‘not guaranteed’ language in benefit statements, when compared to ‘small but very small chance’ language, appeared to increase the perception of likelihood of benefit of entering an early phase trial, especially among those who view their estimates of benefits as “facts.” Such ‘no guarantee’ benefit statements may be misleading and should not be used in informed consent forms.

Keywords

informed consent; benefits statements; early phase trials; research ethics

Early phase intervention trials targeting serious or terminal illnesses continue to engender ethical debate because persons with such conditions represent a particularly vulnerable population of research subjects.¹⁻³ One persistent concern is that patient-subjects overestimate the benefits and that this represents an obstacle to optimal consent.⁴⁻⁷ A review of informed consent forms from 272 phase I oncology studies showed that the forms do not appear to promise excessive benefits, with only 1 instance of a claim of definite direct benefit and virtually all forms (255/272, or 94 percent) communicating uncertainty about benefit.⁸ However, 51% mentioned the possibility of benefit in other parts of the form, including the possibility of cure (5%), prolonged life (19%), or tumor shrinkage (35%).⁸ Another review of consent forms from 321 early phase gene transfer studies confirmed this potentially mixed message regarding benefits of research participation.⁷

Even if a benefit statement does not contain frank misinformation, how the potential for benefit is described may still matter. Consider the following statement from a consent form for a phase I oncology trial: “The possible benefits of this treatment program are greater shrinkage and control of your tumor and prolongation of your life but you understand *this is not guaranteed.*” (Appendix) The use of the phrase ‘not guaranteed’ is in one sense accurate since the investigators cannot “promise or make certain”⁹ that the subjects will benefit. However, in another sense the phrase raises concern since the term ‘guarantee’ is often used in a context where an outcome is likely but merely not certain, as in, “You should pass the test first time, but we can’t guarantee it.”⁹ Thus, some subjects may infer that the probability of benefit from the phase I trial is likely but not guaranteed.

How would potential research subjects interpret such benefit statements? There are potential difficulties to studying actual phase I study participants to answer the question—for example, by randomizing them to two different consent forms and assessing their perceptions of probability of benefit—as it could be seen as manipulating seriously ill, vulnerable patients’ perceptions of benefit. Also, since phase I studies are often small, only relatively large effect sizes would be detectable.

Another complication in interpreting potential subjects’ estimates of probability of benefit is that such numerical estimates are difficult to interpret. When research subjects are asked to estimate the probability of benefit, they often do so not as an expression of mathematical probability but as expressions of hope or wish for luck.^{2,10,11}

We hypothesized that the effect of “not guaranteed” benefit statements is an effect of how language is used rather than a specific effect only present in actual research participants. If

this is correct, it should be possible to show whether such statements induce ordinary (non-patient) competent users of English to perceive higher likelihood of benefit. Thus, we designed an experimental survey to assess this possibility, using a hypothetical scenario of an early phase amyotrophic lateral sclerosis (ALS) clinical trial. To address the issue of the ‘meaning’ of respondents’ numerical estimates, we also examined the relationship between the respondents’ estimates of benefit and their interpretations of those estimates.

Methods

Participants

We recruited subjects through Amazon's Mechanical Turk (MTurk), one of Amazon's web services that allows users to perform tasks (called Human Intelligence Tasks, or HITs, such as participating in web-based experiments) for pay (we paid \$0.50 per subject for this 5 minute survey).¹² MTurk is widely used in experimental surveys in psychology, economics, and political science.^{13,14} All respondents were from the United States and the data were collected anonymously, as Amazon handles the compensation. This study was deemed exempt from federal regulations by the University of Michigan, the University of Rochester, and the NIH.

Procedures

The survey scenario (Appendix) was a hypothetical description of an early phase trial for amyotrophic lateral sclerosis (ALS), a usually terminal, debilitating, and incurable neurological condition. The scenario described the symptoms, prognosis, and the lack of cure for ALS, followed by a description of a first-in-human trial of an experimental intervention. The respondents were told that “In terms of potential benefits to people entering the study, the informed consent document states the following” and then were randomly given one of two statements: In one group (‘no guarantee’ group), the likelihood was described as “It is not guaranteed that you will benefit;” in the second group (control group), the likelihood was described as “There is some but very small chance that you might benefit.”

Respondents were then asked whether, if they had ALS, they would consider participating in the trial, on a 10-point scale (anchored with “would not consider at all”=0 and “definitely would consider”=10). They were then asked: “What would you estimate as the likelihood that your ALS would improve from being in this study?” Their response was recorded on a line ranging from 0 to 100%. Given the literature showing that layperson estimates of probabilities are not always given as expressions of mathematical probabilities,^{2,3,15} we adapted a question from the literature¹¹ and asked a follow-up question: “Which statement below best reflects what you meant by your response to [the question asking for estimate of benefit]?” The 5 response options, whose order was randomized, were: “(1) Those are just the facts; (2) That is what I hope will happen; (3) That is what I fear will happen; (4) It is important to have a positive attitude; (5) There is a lot of uncertainty.” Response options 2, 3, and 4 were derived from the literature showing that people use what appear to be probability estimates to express an emotional attitude or sentiment (hope, fear, or ‘being positive’). We interpreted responses 1 and 5 to mean that persons choosing those options

were in fact attempting to express an estimate of a mathematical probability. Demographic data were also collected.

Analysis

Comparisons of groups were conducted using the chi-square test for categorical variables. Between-group mean difference and 95% confidence intervals were calculated where appropriate.

Results

A total of 584 persons participated in the study (Table 1).

Although the 'no guarantee' group had a slightly greater willingness to consider participating in the ALS study, it was not statistically significant [8.6(SD 1.9) vs 8.3(SD 2.3) on a 10-point scale, $p=0.11$]. However, the 'no guarantee' group's average estimate of likelihood of their ALS improving was significantly higher than the control group's estimate [35.7% (SD 20.2) vs. 28.3% (SD 22.0), $p<0.0001$].

When asked what they meant by their estimates of benefit, the two groups' response distributions were similar (Table 2).

When the two arms are combined, about half (47%) of subjects chose response options representing expressions of sentiment. Only 16.5% chose "Those are just the facts." The most common response option at 36.1% was "There is a lot of uncertainty."

Table 3 shows the difference in estimates of likelihood of benefit between the two arms according to the respondents' stated meaning of the likelihood estimates. Among those who chose "Those are just the facts" or "There is a lot of uncertainty," those exposed to 'no guarantee' benefit language had higher estimate of benefit than the control group. The same pattern is seen among those who said "This is what I fear will happen," although the confidence interval for the difference is large (and includes no difference) because of the small number of respondents in that group. Those who said they meant "This is what I hope will happen" or "It is important to have a positive attitude" expressed higher estimates of likelihood of benefit when compared with others [40.7% (SD21.4) vs 25.4% (18.9), $p<0.0001$], but their estimates differed by only about 3% between the two arms receiving different benefit statements.

Discussion

In this experiment, subjects receiving a benefit statement containing "it cannot be guaranteed" had a significantly higher estimates of likelihood of benefit than those receiving "some but very small chance" language. Further, a follow up question asking the respondents to indicate what they meant by their estimate of benefit resulted in a more complex and in some ways more worrisome finding.

The results show that, consistent with other studies, laypersons may not always use numerical probability estimates to express mathematical quantities of fact but often use them

to serve other functions.^{2,11,15,16} In our study, nearly half of the subjects chose response options having to do with expressions of sentiment (hope, fear, need to stay positive). When compared to people choosing other response options (“just the facts” and “lot of uncertainty” responses), those who chose either “hope will happen” or “need to stay positive” gave higher estimates of benefit. But the benefit statement manipulation had no significant impact on the likelihood estimates of those who responded that such estimates are expressions of positive sentiments.

The worrisome finding is that it is those who took themselves to be reflecting “just the facts” or that “there is a lot of uncertainty” with their estimates—thus, in our view, attempting to express a probability estimate of what is likely to actually happen—gave higher estimates of benefit when exposed to the “It cannot be guaranteed” statement. For those who are attempting to estimate the actual probability of an event, the ‘not guaranteed’ statement may indeed change the perception of likelihood of benefit significantly. These two response groups constitute 52.7% of subjects; thus, a majority of people's estimates of actual likelihood of benefit may be affected by statements such as “it cannot be guaranteed that you will benefit.”

We note several limitations. First, the design of this study allowed us to detect an effect of certain use of language among relatively young competent English users whose health experience is unknown. The results therefore cannot be taken as direct evidence of how actual research subjects with serious illnesses would perceive the potential benefits of phase I trials. But there is no reason to suppose that persons with serious illnesses entering phase I studies would be immune to this effect of language use. Also, there are probably many factors beyond the language used in consent forms that go into actual participants' perceptions of benefit. Second, we used a one-page description of the phase I study for ALS, not an actual informed consent form, thus making the benefit statement quite noticeable. Since in an actual trial subjects may not be cued to the benefit statements, the effect in actual studies may differ. Third, we cannot rule out that the benefit statement used in the comparison group (i.e., “very small chance” statement) had an effect of deflating the benefit estimates. Nevertheless, the overall result shows, other things being equal, that benefits language does make a difference. Fourth, because we only offered five close-ended response options regarding what the respondents meant by their benefit estimates, we may not have captured all possible interpretations. Finally, this study did not show that benefit statements have an impact on willingness to consider participating in the ALS clinical trial.

This experiment provides evidence against the use of statements like “it is not guaranteed” in describing potential benefits of phase I studies targeting seriously ill populations. Eliminating frank misinformation on informed consent forms is important but other preventable, subtle misunderstandings may also need to be considered. For instance, other statements such as, “This research study includes procedures which may not give you immediate benefits” could be misleading even if technically accurate, since some may read it to mean later (not immediate) benefits are likely.

In conclusion, this study provides evidence that some types of benefit statements—such as “it cannot be guaranteed” statements—in phase I informed consent forms could induce

subjects to perceive higher likelihood of benefit than they otherwise would. While appearing to convey a negative message intended to limit subject expectations, such statements in fact may have the opposite effect and their use should be discouraged.

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Appendix

ALS Scenario Description

Imagine that you have ALS (amyotrophic lateral sclerosis, also known as Lou Gehrig's Disease). In ALS, nerve cells waste away so that they can no longer send messages to your muscles. Eventually your muscles will become so weak that you won't be able to move your arms, legs, and other parts of your body. ALS gets worse over months to years until you're paralyzed and cannot care for yourself. Eventually you'll lose the strength to swallow and breathe. Most of the time, thinking is not changed, but there's a small chance you'll develop dementia. Death usually occurs within 3 - 5 years of diagnosis. You could try to prolong your survival by using artificial means, but this would require using a feeding tube and ventilator support (lung machine).

You were diagnosed with ALS about 1 year ago.

There is no cure for ALS. There is one FDA approved drug but it does not work very well. You have tried this drug but it has not helped. You feel like you've run out of options.

But then your doctor brings up the possibility of participating in a research study. Your doctor, who is an ALS researcher, asks you if you would like to participate in a research study testing an experimental drug called TC10.

The researchers have done some genetic testing to better characterize your ALS and believe that there are scientific reasons to use TC10 to target your ALS. Also, animal experiments have shown TC10 to be promising. But the reality is that researchers do not know how humans will respond to this drug. That is why they are doing this research.

In terms of potential benefits to people entering the study, the informed consent document states the following: [subjects are randomized to one of the two arms below]

Arm 1: "It is not guaranteed that you will benefit."

Arm 2: "There is some but very small chance that you might benefit."

The study you're being asked to enroll in is a small study to see if TC10 has serious side effects and to see if it has promise as a treatment for ALS, in order to find out if larger studies should be conducted.

Examples of ‘not guaranteed’ language from phase I trial consent forms

The use of ‘not guaranteed’ language is not unusual in early phase clinical trials involving patient-subjects. For example, King et al. found that such phrases are common in early phase gene transfer trial informed consent documents.⁷ Below are examples of such language from informed consent forms of phase I oncology trials from 3 different academic medical centers.*

Institution	Protocol	Statements re: Benefit
[on file]	A Phase I Study of [on file] in Combination with [on file]	My doctors cannot and do not guarantee I will benefit if I take part in this study. The treatment I get may even be harmful, [in introduction on page 1]
[on file]	Phase 1B/IIA Pharmacokinetics/ Pharmacodynamics Study of [on file] in Patients with Newly Diagnosed Head and Neck Cancer.	THE POTENTIAL BENEFITS TO YOU OR THE OTHERS ARE: It is not possible to predict whether or not any personal benefit will result from the use of the treatment program... The possible benefits of this treatment program are greater shrinkage and control of your tumor and prolongation of your life but you understand this is not guaranteed.
[on file]	A Phase I Dose-Escalation Trial of Combined Therapy with [on file] and Radiotherapy in Patients with Solid Malignancies	Possible Benefits: If the test drug is effective, you may benefit by having an improvement in your disease status. It is possible, however, that no therapeutic or other direct health benefits may result during or following completion of this study. Since we have very limited information on the drug's effect on cancer in humans, we do not guarantee that you will benefit from taking part in this study, although the knowledge gained may benefit others. The drug you receive may even be harmful. (benefits section- page 6)

* From NIH Department of Bioethics database of phase I oncology informed consent forms.

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Table 1

Comparison of respondent characteristics by benefit statement arm.

	It is not guaranteed that you will benefit. n=294^a	There is some but very small chance that you might benefit. n=290^a
Age, mean (SD)	33.4(11.5)	32.0(10.9)
Women	39.9% (117/293)	35.9% (102/284)
Race (Could select more than one) ^b		
White	82.0% (241)	82.4% (239)
Black/African-American	8.8% (26)	7.6% (22)
Asian/Asian-American	8.5% (25)	7.6% (22)
American Indian/Alaska	1.4% (4)	4.5% (13)
Native	1.7% (5)	0.3%(1)
Other		
Hispanic	6.1% (18/293)	5.3% (15/284)
Education		
Less than college	45.1% (132)	46.1% (131)
College grad	41.3% (121)	35.9% (102)
More than college	13.7% (40)	18.0% (51)
Income		
<20K	22.5% (66)	20.8% (59)
20-40K	31.4% (92)	26.5% (75)
40-60K	16.0% (47)	19.8% (56)
60-100K	20.5% (60)	22.6% (64)
>100K	9.6% (28)	10.2% (29)

^aSome row totals do not add to 294 and 290 because of missing data for that variable.^b Respondents were permitted to choose more than one race category; thus, a group test was not performed.

Table 2

Comparison of distribution of response to “Which statement below best reflects what you meant by your [estimate of likelihood of benefit]?” by benefit statement arm.

Benefit statement\Response	It is not guaranteed that you will benefit, n=293 % (N)	There is some but very small chance that you might benefit, n=288 %	p-value
Those are just the facts	16.0 (47)	17.0 (49)	0.68 ^a
This is what I hope will happen	19.1 (56)	17.0 (49)	
This is what I fear will happen	3.4 (10)	3.8(11)	
It is important to have a positive attitude	27.6(81)	23.6 (68)	
There is a lot of uncertainty	33.8 (99)	38.5(111)	

^a χ^2 test.

Table 3

Comparison of respondents' estimates of % likelihood of benefit between the two benefit statement arms, according to their interpretations of what the estimate means.

Benefit statement\Interpretation of estimate of likelihood of benefit	It is not guaranteed that you will benefit (n=293) Mean% (SD)	There is some but very small chance that you might benefit (n=288) Mean% (SD)	Between-arm Difference (95% CI)
Those are just the facts (N = 96)	31.0(22.4)	18.9 (21.0)	21.1 (3.3, 20.9)
This is what I hope will happen (N = 105)	40.7(19.7)	37.4 (22.7)	3.3 (-4.9, 11.5)
This is what I fear will happen (N = 21)	27.9 (18.0)	15.2 (12.9)	12.7 (-1.5, 26.9)
It is important to have a positive attitude (N = 149)	43.1 (19.8)	40.0 (23.7)	3.1 (-3.9, 10.1)
There is a lot of uncertainty (N = 210)	29.9 (17.3)	22.6 (16.6)	7.3 (2.7, 11.9)