

Uncertain Benefit: Investigators' Views and Communications in Early Phase Gene Transfer Trials *

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We report on a study of potential sources of therapeutic misconception in early phase gene transfer research, examining how investigators and their consent forms represent the prospect for direct benefit. Our analysis demonstrates that even though half of PIs said they expected direct medical benefit for their subjects, they did not necessarily convey this to their subjects. What they reported telling subjects resembled what was written in their consent form, which suggests that, far from being irrelevant, the consent form is an influential component of the consent process. We also demonstrate that the language used to describe direct benefit in consent forms and PIs' discussions was mostly vague, ambiguous, and indeterminate about benefit, rather than clearly negative. This was especially true for cancer and vascular disease trials. Our respondents found the problem of balancing hopes and expectations, for themselves and for their subjects, extraordinarily challenging. In the current era, investigators face such challenges without consistent normative guidance or agreed-upon standards for how to talk about scientific promise and uncertainty in early phase trials. This dilemma cannot be effectively addressed by individual investigators alone, but must be acknowledged and openly discussed by the scientific community at large.

Key Words: gene therapy, clinical trials phase I/*standards, disclosure, ethics medical, informed consent, interviews, research/*standards, researcher–subject relations, uncertainty

INTRODUCTION

Since the first application of gene transfer in human trials in the early 1990s, over 500 studies have been conducted in a broad array of disease categories, including cancer, monogenic diseases, infectious diseases, cardiovascular and peripheral artery diseases, and others. The promise of “gene therapy” generated great enthusiasm [1], but by the mid-1990s, the field experienced disappointing results in clinical trials, difficulty translating animal data to humans, and vector problems [2]. An NIH report [3]

criticized the “overly optimistic public portrayal of gene transfer experiments and unsubstantiated claims of efficacy” [4–7]. Thus, well before the death of Jesse Gelsinger in a gene transfer trial in 1999, concern about overselling this new technology—often blamed on investigators—raised questions about the ability of subjects, the public, and even IRBs and the biomedical community to define, discuss, and evaluate its benefits and risks [5,8].

Almost all gene transfer research (GTR) trials are early phase studies. Nearly three-quarters are also oncology trials, in which subjects' misunderstanding of the purposes and potential risks and overestimation of the potential for direct medical benefit from early phase research have been identified [9,10]. Investigators' own beliefs about the purposes of clinical research and potential for direct benefit to subjects have not been

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examined as carefully. The most comprehensive study is a survey of 547 oncologists in which “many respondents viewed the main societal purpose of clinical trials as benefiting the participants rather than creating generalizable knowledge to advance future therapy” [11]. The authors express concern about investigators’ tendency to conflate research and treatment, but do not address whether and how investigators’ *views* about potential direct benefits for subjects affect their *communications* (in the consent forms and process) with study subjects.

Do investigators in early phase gene transfer trials expect direct medical benefit from the experimental intervention for their subjects? How are their own views related to their communications about direct benefit, that is, what they say they tell subjects and what is offered in their consent forms? If direct benefit is expected, what language is used to describe its likelihood and nature? To answer these questions, we present quantitative and qualitative data from in-depth interviews with recent GTR investigators and from their consent forms. The 39 trials examined are representative of all GTR in the US with regard to disease category and phase designation. Because the investigators we interviewed have considerable experience not only with GTR but in other types of clinical trials, our findings are potentially relevant for investigators and review boards involved in early phase clinical research more generally.

RESULTS

Principal Investigators’ (PIs’) Views about Direct Benefit For Subjects

Likelihood of direct benefit expected. Responses to the question, “Do you expect that the intervention in the

TABLE 1: Assessment of likelihood terminology in interviews and consent forms

Likely	I expect it will Very good chance [Benefit] should happen
Unlikely	I do not expect that Unlikely Remote chance Absolutely not This is not [benefit] Direct benefits are unlikely We do not anticipate that you will have any benefit from participating
Indeterminate likelihood	If [X] happens, then maybe It’s possible There’s a chance Promising We hope this will help There is no guarantee May or may not help We cannot tell whether you will benefit

[GTR study] will have a direct medical benefit for subjects?” ranged from certainty that direct medical benefit *would not* occur (“no, there is no expectation because there’s no prior data”), to certainty that it *would* (“absolutely—I wouldn’t be doing this if I didn’t think so”) (Table 1). Forty-one percent ($N = 16$) said “no,” while the rest said “yes” ($N = 18$) or “don’t know” ($N = 5$) (Table 2). More than one-third of investigators qualified their yes-or-no responses with indeterminate likelihood language such as “it is conceivable”

Q: Do you expect that the gene transfer intervention in the [study] will have a direct medical benefit for subjects?

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.

FIG. 1. Interview excerpt.

TABLE 2: Distribution of assessment of likelihood in PI view, PI discussion, and consent form by phase and disease type (N = 39)

	Total	PI view		PI discussion		Consent form	
		Doesn't expect	Does expect/DK	Unlikely	Indeterminate	Unlikely	Indeterminate
Total	100% 39	41% 16	59% 23	36% 14	64% 25	26% 10	74% 29
Phase of study							
Phase I	100% 21	43% 9	57% 12	57% 12	43% 9	43% 9	57% 12
Phase I/II–II	100% 18	39% 7	61% 11	11% 2	89% 16	6% 1	94% 17
Relationship		$\gamma = 0.08, P(\chi^2) = 0.80$		$\gamma = 0.83, P(\chi^2) = 0.003$		$\gamma = 0.85, P(\chi^2) = 0.008$	
Disease category							
Infectious or monogenic	100% 11	64% 7	36% 4	64% 7	36% 4	55% 6	45% 5
Cancer or vascular	100% 28	32% 9	68% 19	25% 7	75% 21	14% 4	86% 24
Relationship		$\gamma = 0.57, P(\chi^2) = 0.07$		$\gamma = 0.68, P(\chi^2) = 0.024$		$\gamma = 0.76, P(\chi^2) = 0.01$	

γ is a measure of association used with categorical data, interpreted like a Pearson's correlation coefficient.

or “there may be some responders” or “there was a chance.” Some talked about their hopes for benefit to subjects: “Yes, that’s what we hope for” or “No . . . hope that it will, yes, but we weren’t counting on it.” And some investigators found the question difficult to answer (see Fig. 1).

Why do some investigators say they expect direct benefit and others do not? Disease type may play a role. Table 2 shows that PIs conducting cancer and vascular disease trials were more likely to answer “yes” than those conducting monogenic and infectious disease trials ($\gamma = 0.57$, Table 2). PIs’ expectations about direct benefit were not related to study phase; that is, PIs conducting phase I studies were just as likely to answer “yes” (or “no”) as those conducting phase I–II and II trials (Table 2). In addition, different PIs conducting phase I trials using the same type of gene transfer intervention for the same disease population often differed in their expectations about the likelihood of direct benefit.

Divergent views about scientific promise and uncertainty seem to explain some of the variation. “Yes” answers were often justified by citing encouraging preclinical or other clinical evidence (e.g., “[we expected] immune response based on preclinical evidence”), whereas a “no” response might be explained by uncertainty inherent in study design (e.g., “No, this is a safety trial . . .” or “It’s not powered to detect [benefit]”).

Nature of direct benefit expected. The PIs who said they expected direct benefit were asked what they expected and why. All but one described the direct benefit that they expected as surrogate endpoints, such as anti-tumor response or change in lab values. About half also linked changes in surrogate endpoints to desired clinical out-

comes (e.g., “Have patients’ tumors shrink [surrogate] and have people live longer [clinical]” or “Some increase in clotting factor level [surrogate] . . . and that might translate into a smaller amount of factor that would be needed [clinical] or a fewer number of hemorrhages [clinical] potentially”) (Table 3).

Communications with Subjects about Direct Benefit in Discussions and Consent Forms

Communications about likelihood. PIs were asked, “How did you discuss the possibility of direct benefit from the gene transfer intervention with your subjects?” and their answers were assessed for a message that suggested overall likelihood. Thirty-six percent reported that they described direct benefit to subjects as unlikely or not expected; the remaining two-thirds described benefit using only indeterminate language (Table 2). While a few PIs described the possibility of some type of direct benefit to subjects as likely, these statements were invariably mixed with indeterminate and unlikely language; no PIs said they communicated an overall message that direct benefit was likely.

Similarly, 26% of the consent forms described direct benefit as unlikely, using a combination of unlikely and indeterminate statements (Table 2). Only one consent form, for a phase I monogenic disease trial, used no indeterminate likelihood language and conveyed throughout that benefit was not expected. Seventy-four percent of the consent forms did not clearly convey that benefit was unlikely and used likelihood language that was indeterminate overall. Indeterminate statements were especially common in the Benefit sections (e.g., “It is not possible to predict or guarantee a

TABLE 3: Nature of benefit terminology in interviews and consent forms

Surrogate endpoint: laboratory measurement that stands in statistically for a clinical endpoint	Tumor shrinkage Have the vector produce factor Boost the immune system Stimulate anti-tumor response Grow new blood vessels "...cancer cells will be exposed to the gene and take up the gene" Keep the tumor localized
Clinical endpoint: specific benefit that can be felt or experienced by subjects	Longer survival Eliminate the pain that they are having Decrease severity of infections Restore normal circulation Avoid amputation Reduce complications of chemotherapy "...delay the natural progression of the disease to the point where the men can have a very good quality of life"
Vague clinical endpoint: vague general statement alluding to clinical benefit, which appears to provide information about what subjects might feel or experience but is susceptible to multiple interpretations by potential subjects	Decrease symptoms Therapeutic option Getting a response
Contentless benefit: no nature information, empty statement	Positive results Benefit Direct benefit True benefit Help

positive response to treatment" or "You may receive no benefit at all from the study treatment"). No consent forms conveyed an overall assessment that direct benefit was likely.

Two-thirds of PIs reported discussing scientific design and evidence from other clinical or preclinical laboratory studies with subjects. Such information and evidence were also found in the Background/Purpose sections of their consent forms. Scientific promise could be presented with optimism ("animal studies are suggestive ... there's another study using a different, [but] very similar ... gene and using similar technique, and they suggest that its patients are feeling better") or caution ("I emphasized that while we have had very positive results in the preclinical studies, that it was very difficult to expect that that would happen in the phase I study").

PIs also reported that they discussed hope for benefit with subjects, even when the overall benefit message was unlikely: "The hope would be for patients that their [endpoint] remain stable and their disease does not progress" or "We were obviously hopeful that that would occur; realistically it was not something we expected, and that's exactly as we described to patients." Similarly, examples from the consent forms described hoped-for outcomes as well as hope contrasted with more realistic predictions: "The hope is that we can improve your symptoms and prolong your survival with this treatment" or "While the investigators hope that my tumor will decrease in size or even go away, I have not been promised or extended a promise of any kind that this treatment will be helpful in my case. It could even make my disease worse and I am consenting to participate knowing this ahead of time."

For one PI, addressing both hope and expectation did not seem problematic:

Expecting it and hoping for it are two different things. If we've done our job right, they [subjects] don't expect it, but they hope for it. But I think they hope for it because we tell them that it's possible. With the scientific evidence so far [we] would say it's possible.

Some PIs, however, expressed concern about subjects' unrealistic expectations, that "despite the fact that they are told very directly [that they will not benefit], some participate because they think it will improve their clinical course."

Communications about nature of direct benefit. In reports on how they discussed direct benefit with subjects, PIs used terms from all four of our nature categories: surrogate, clinical, and vague clinical endpoints, and contentless terms (Table 3). Types of benefit were always linked to different likelihood terms, as illustrated in the following example.

I say that there is a possibility [*indeterminate*] that new blood vessel growth [*surrogate*] will occur and if it does occur [*indeterminate*], we are talking about very small blood vessels, and our goal is to heal [*clinical*] ... and to eliminate the pain [*clinical*] that they are having. That we will not [*clearly unlikely*] restore normal circulation [*clinical*], even if [*indeterminate*] we have a remarkable success [*contentless*].

All consent forms in our sample described surrogate endpoints as direct benefits, while one-third also offered clinical endpoints such as "increase in life span" or vague clinical endpoints like "improve [organ] disease."

Congruence of PIs' Views about Likelihood of Direct Benefit and Communications with Subjects

There was a strong correlation between the two "public" communications about likelihood of direct medical benefit. In 33 of the 39 studies (85%), the consent form and the reported discussion with subjects conveyed congruent assessments of benefit likelihood. That is, both said that benefit was unlikely or both did not ($\gamma = 0.95$, Table 4). Some PIs said they tied their discussion closely to the consent form: "I mostly speak to the same sort of elements you'd see in a consent form, really." When there was disagreement between consent forms and discussions, the PI's description of benefit discussion was usually more discouraging than likelihood assessments in the consent form (Table 4).

In contrast, PIs' own views were not correlated with likelihood of direct benefit presented in consent forms and discussions with subjects (data not shown). No communication to subjects in reported discussions and in consent forms presented direct benefit as likely, whereas many PIs said they expected direct benefit. This public-private "disconnect" about likelihood could be quite pronounced, as articulated by one PI:

I'm not allowed by the IRB to suggest to the patients that there might be therapeutic benefit. In my heart of hearts, I think these cells are going to kill [cancer] cells ... however, I was required by my IRB to put into the consent form a statement to the effect that this will not help the patient who consents to be in their study, because it's a phase I.

In addition, the public communications were more clearly negative in infectious and monogenetic disease trials and in phase I studies, whereas PIs' own views were related only to disease, not to phase (Table 2). Taken together, these findings suggest that PIs' views about the likelihood of direct medical benefit in early phase trials are distinct from what they or their consent forms communicate to subjects.

TABLE 4: Distribution of likelihood assessments in consent form by discussion with subjects (cell percentages shown)

Discussion	Consent Form	
	Unlikely	Intermediate
Unlikely	23% 9	13% 5
Indeterminate	3% 1	62% 24
Column total	26% 10	74% 29
Relationship	$\gamma = 0.95$	$P(\chi^2) = 0.000$

γ is a measure of association used with categorical data, interpreted like a Pearson's correlation coefficient.

Only 9 of the 39 studies clearly conveyed that direct benefit was unlikely in both consent forms and reported discussions with subjects (Table 4). Five of the nine PIs expected direct benefit; the others did not. Regardless, their communications projected that subjects should not expect it, in no uncertain terms: "I say very specifically ... that you will not have a direct benefit from participation in this trial" or "I was very explicit that they could not expect to receive direct medical benefit, that this was not the way this study was designed." One PI went on to offer one of the rare normative statements about discussion of the potential for benefit: "... there was one institution where an investigator had been caught on a phase I study, telling patients that it was going to help them, and I pointed out this was unethical; we were not doing this."

DISCUSSION

Our analysis demonstrates that even though half of PIs in this diverse sample of early phase gene transfer studies said they expected direct medical benefit for their subjects, they did not necessarily convey this to their subjects. What they said they told subjects resembled the consent form more than their own views. In addition, PIs said they relied on the consent form in their discussion of benefits and risks. These findings suggest that, far from being irrelevant to the consent process, the consent form is an influential component. They also suggest that at least some PIs are able to separate their personal hopes and expectations about direct benefit from how they present information to subjects. They may do so to promote subjects' best understanding, or simply to obey their IRBs, but whatever the reason, we should not assume (as some studies have) that their views will be communicated to subjects.

While consent forms and PIs' discussion of benefit were often consistent with each other, usually this was because both were vague, ambiguous, and indeterminate about benefit, rather than clearly negative. Even statements intended to discourage expectation of benefit—e.g., "we do not guarantee or promise"—do not state clearly that benefit is unlikely. PIs' likelihood language seems to reflect a struggle between two opposing impulses: don't overpromise and don't take away hope [9,12–19]. There is no clear resolution to the underlying normative question: what *should* investigators communicate about the potential for direct benefit to subjects in early phase clinical research? At present, it appears that this struggle is temporarily resolved through avoiding the real question: how likely is it that an individual subject will receive benefit from an early phase experimental intervention? Vague, ambiguous, and indeterminate language is appropriate in a scientific context but not in a quasi-clinical context, in which patients are seeking treatment.

The pervasive description of surrogate endpoints as potential direct benefits is also cause for concern. While surrogate endpoints are appropriate as scientific objectives in GTR protocols, they may not be as descriptions of potential direct benefit. When surrogate endpoints are described as potential benefits in consent forms, we caution that subjects might view them as clinically meaningful, which in most cases should not be assumed. For example, when PIs state, "We thought that it might, in theory at least, augment the immune system," subjects might too readily conclude that augmenting the immune system will improve their medical condition. "Tumor shrinkage" or "tumor response"—important scientific endpoints to measure in a research protocol—could imply to laypersons the control or elimination of their cancer. If PIs described the potential relationships between surrogate and clinical endpoints in clear and specific terms, however, the potential for subjects to overestimate direct medical benefit would probably decrease considerably.

Despite increased scrutiny of GTR by local institutions and federal agencies since Jesse Gelsinger's death, there is no consensus about how to represent clearly the potential for direct benefit. In our examination of 321 GTR consent forms (N. M. P. King *et al.*, submitted for publication), we found that both direct benefit descriptions and language referring to investigators, subjects, and the gene transfer intervention were often variable and inconsistent across consent forms, in ways that could confuse subjects or even promote overestimation of potential direct benefit. IRB representatives also vary considerably in their views about whether and how direct benefit should be described [20]. Some IRB respondents considered it unethical to advertise any potential benefit in early phase trials, whereas others stated that research without the potential for direct benefit to subjects should not be approved. If PIs are not all in perfect agreement about how to view and describe potential direct benefit in early phase GTR, they appear to be in good company.

Our respondents found the problem of balancing hopes and expectations, for themselves and for their subjects, extraordinarily challenging. It was difficult for them to communicate about direct benefit using clear and consistent language about the nature and likelihood of benefit, and much of what is said and written is vague and possibly misleading. PIs conducting early phase clinical trials face the challenge of communicating about benefit without consistent normative guidance from local or federal review bodies. Nor are there agreed-upon standards among clinical researchers and scientists for how to talk about scientific promise and uncertainty in early phase trials. This dilemma cannot be addressed by individual PIs alone, but must be acknowledged and openly discussed by the scientific community at large.

Although this study is based on a carefully selected, representative sample of all GTR ongoing between 1999

and 2002, it has several potential limitations. The first involves the use of investigators' self-reports to represent discussions with subjects. A more direct measure of PI discussions could be obtained from direct observation of subject recruitment interviews; however, our approach allowed us to obtain a larger sample than would have been otherwise feasible. A second possible limitation is the influence of social desirability on responses to some interview questions, that PIs would tell us they discussed benefit in a more clear and discouraging way than they actually did, especially because our interviews were conducted at the beginning of the period of heightened scrutiny of GTR after Jesse Gelsinger's death. Instead, many PIs engaged with interviewers actively and thoughtfully about the challenges inherent in discussions of early phase GTR. Overall, the strength of our findings lies not in statistical analyses, but in the careful documentation of language used by PIs and in consent forms to define and discuss the dimensions of direct benefit in gene transfer research.

DESIGN AND METHODS

Sample. We contacted PIs of 123 clinical trials included on the Office of Biotechnology Activities (OBA) gene transfer protocol list between December 1998 and December 2000 as early phase "therapeutic" GTR studies with adults between December 1998 and December 2000. Seventy-eight of the 123 trials were found to be eligible for recruitment; of these, 39 PIs (50%) were interviewed. The phase designation and disease type of the 39 trials are largely representative of all GTR studies on the OBA list between 1990 and 2001 (Table 5). Two-thirds were cancer trials, over half were phase I studies. The median number of subjects in our sample of studies was 7 (range 1–63). All 39 PI respondents were physicians, 8 also had a Ph.D., and all but 3 reported ongoing clinical responsibilities. Their mean age was 45; 77% were male. All had considerable experience conducting clinical trials, and 50% had conducted other gene transfer trials.

TABLE 5: Distribution of total GTR protocols, eligible trials, and study samples by disease and phase

Study characteristics	Total GTR protocols 1990-2001 (N = 457)	Eligible GTR studies* (N = 78)	Studies with PI interviews (N = 39)
Total	457 (100%)	78 (100%)	39 (100%)
Phase			
I	–	44 (56%)	22 (56%)
I/II	–	13 (17%)	6 (15%)
II	–	21 (27%)	11 (28%)
Disease			
Cancer	314 (69%)	57 (73%)	25 (64%)
Monogenic	54 (12%)	7 (9%)	7 (18%)
Infectious	37 (8%)	5 (6%)	4 (10%)
Vascular	52 (11%)	9 (12%)	3 (8%)

Percentages may not add up to 100 due to rounding.

*Between 12/1998 and 12/2000.

Methods. The 45-min telephone interviews were conducted by two of the authors (G.H. and A.D.) between July 2000 and July 2002. Researchers were asked to describe their experiences conducting a particular GTR trial; the purpose of their study; expectation of direct benefit for subjects from the intervention; other possible benefits (e.g., inclusion or collateral benefits derived from being on study and aspirational or societal benefits [8]); possible risks to subjects; why they thought subjects joined the study; how direct benefit, other benefits, and risks were discussed with subjects; and whether they viewed their role in the study as mostly taking care of patients or mostly conducting research.

The final, IRB-approved consent forms used in the 39 trials were obtained from the investigators, who gave permission to link the consent form analysis to interview data. Consent forms were coded by three of the authors (N.K., G.H., and A.D.) using a 94-item coding form developed for assessment of all GTR consent forms, with additional direct benefit assessment codes (N. M. P. King *et al.*, submitted for publication). The project was approved by IRBs at the University of North Carolina and the National Human Genome Research Institute. Interview and consent form instruments are available at <http://socialmedicine.med.unc.edu/scob/>.

Measurement of direct benefit. We asked PIs about their own views: "Do you expect that the intervention in the [GTR study] will have a direct medical benefit for subjects?" Those who said "yes" were asked what they expected and why. Those who said "no" sometimes offered more explanation, but were not probed further. These were understood to be questions about the *likelihood* that a direct medical benefit will occur and the *nature* of that benefit and coded accordingly (see Tables 1 and 3). The same coding categories of likelihood and nature of benefit were also used to assess responses to the question about *communication* with subjects ("How did you discuss the possibility of direct benefit from the gene transfer intervention with your subjects?") and to categorize *written communication* about benefit in the consent forms.

Three categories of likelihood of direct benefit were identified: clearly likely, clearly unlikely, and indeterminate. Indeterminate likelihood expressions included language that appeared to express genuine uncertainty, such as "may or may not"; text that was encouraging but not explicit, such as "it's possible"; text that might seem to discourage benefit but was not explicit, such as "no guarantee"; and expressions of hope (Table 1).

Answers to the question of whether PIs themselves expected direct benefit were "yes," "no," or "don't know" (when they would not make a choice); qualifications of these responses were coded separately. An overall likelihood category was applied to each description of discussions with subjects and to consent forms. To minimize bias in the direction of the hypothesis that PIs might oversell the potential for direct benefit, the overall unlikely category was applied in nearly all instances in which an "unlikely" statement was coded anywhere in the PI's discussion or consent form.

We coded the nature of direct medical benefit described in consent forms and interview transcripts using four categories: surrogate endpoints, clinical endpoints, vague language suggestive of clinical endpoints, and "contentless" language that provides no information about the nature of any expected benefit (Table 3). In most cases, when PIs mentioned a type of benefit they also talked about how likely it was to occur. These could be highly specific about both nature and likelihood ("we expect [clearly likely] to grow new blood vessels [surrogate]) or quite vague ("it may [indeterminate] help [contentless]).

Analysis. Consent forms were assessed by two coders, and the reconciled codes were entered into a data file. Kappa scores, measuring coder agreement, were within the moderate range [21]. Quantitative interview data were entered directly into a computer-assisted telephone interview software program. Qualitative analysis of interview transcripts focused on responses to eight questions that elicited information on direct benefit. These were coded in teams of at least two co-investi-

gators, and differences were reconciled in groups of four [22]. Codes were entered into an N6 text program and linked to both the quantitative interview and the consent form data in Stata. Cross-tabulations were used to compare data on PIs' views and communications about direct benefit. While we include tests of statistical significance, we focus more on descriptive results because of our small sample size and the richness of our qualitative data.

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