

Special Article

DESCRIPTIONS OF BENEFITS AND RISKS IN CONSENT FORMS FOR PHASE 1 ONCOLOGY TRIALS

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ABSTRACT

**Background** Ethicists have suggested that written consent forms encourage participants in phase 1 cancer trials to expect benefit from the experimental agent and to overlook serious risks.

**Methods** To evaluate the written description of direct benefit as well as risk, all consent forms for 1999 phase 1 cancer trials were compiled from 80 percent of the National Cancer Institute–designated cancer centers and from six of eight large pharmaceutical developers of anticancer drugs. In each case, we evaluated the characteristics of the trial, the descriptions of the purpose and procedures of the research, the promise of benefit, the description of risks, and the description of alternatives.

**Results** Of 272 forms, 268 explicitly mentioned that the trial was research, and 249 stated that the purpose of the trial was testing for safety. Nearly all forms (269) mentioned the right to withdraw from the trial. Almost all forms (260) referred to the experimental agent as “treatment” or “therapy.” Only one consent form promised direct benefit to subjects. Most forms (181) mentioned death as a risk, and very few (14) mentioned cure as even a possible benefit. Most (229) stated that there was unknown risk involved and indicated that severe or permanent harms were possible (224).

**Conclusions** Consent forms for phase 1 oncology studies almost never promise direct benefit to subjects, rarely mention cure, and usually communicate the seriousness and unpredictability of risk. Although there is room for improvement, the substance of these forms is unlikely to be the primary source of misunderstanding by subjects in phase 1 oncology trials. (N Engl J Med 2002;347:2134-40.)

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THE main objective of phase 1 oncology trials is to determine the maximal safe dose of an investigational agent that may never have been previously tested in humans. Consequently, the prospect of direct clinical benefit to patient-subjects may be extremely low, whereas the risks may be substantial and the possible harms severe.<sup>1-7</sup> Meta-analyses place the average response rate for phase 1 oncology trials at less than 6 percent and the

rate of death from toxic effects at approximately 0.5 percent.<sup>8-11</sup>

The few empirical studies that have been conducted of subjects in these trials suggest that many subjects do not understand critical aspects of the research.<sup>12-16</sup> Only one third of the subjects could identify the purpose of a phase 1 cancer trial as safety testing, and most of them anticipated clinical benefits such as tumor shrinkage and decreased symptoms.<sup>12-16</sup>

Many commentators have expressed ethical concerns about informed consent in phase 1 trials.<sup>3-5,12,17-20</sup> According to Gary Ellis, former director of the U.S. Office of Protection from Research Risks, 90 percent of the misunderstandings of subjects about phase 1 trials “reveal problems with informed consent.”<sup>19</sup> It has been suggested that consent forms for phase 1 cancer trials distort information in order to increase enrollment,<sup>19,20</sup> make the tested agents “sound like the cure for cancer,”<sup>19</sup> and “may actually be interfering with what might otherwise be an ethically appropriate informed consent process.”<sup>20</sup>

Consent documents play an integral part in the process of obtaining informed consent. Subjects gain a better understanding of the trial by a consent form and an interview than by an interview alone.<sup>21</sup> Such forms serve as guides for discussions between the research team and the subject and as a reference that is always available to the subject.<sup>22</sup> Because they record a signature, these forms also provide legal and symbolic documentation of an agreement to participate. Consent forms are subject to scrutiny by both regulators and third parties, especially when problems arise.<sup>23,24</sup> The substantial effort expended by investigators, members of institutional review boards, regulators, and others in writing and reviewing consent forms reflects their importance as a necessary source of information for subjects.<sup>25</sup>

The readability of consent forms for research in oncology has been investigated previously,<sup>26,27</sup> but

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their substantive content has not. In this study, we analyzed the way in which consent forms for phase 1 oncology trials describe the purpose, benefits, and risks of the research and possible alternatives to participation.

## METHODS

### Accrual of Consent Forms

Consent forms for all phase 1 oncology trials conducted in 1999 were requested from the 52 National Cancer Institute (NCI)-designated cancer centers<sup>28</sup> and from 10 of the largest manufacturers of anticancer drugs in the United States.<sup>29</sup> Six of the NCI-designated cancer centers and two of the drug manufacturers performed no such trials in 1999. The response rates were 80 percent among the cancer centers (37 of 46) and 75 percent among the pharmaceutical companies (6 of 8). Only consent forms for protocols testing anticancer agents were used in this study; forms for other phase 1 cancer protocols, such as those testing supportive care, were excluded. The sample consisted of 246 consent forms from cancer centers and 26 from pharmaceutical companies. The number of consent forms from each institution ranged from 1 to 28 (mean, 6.3; median, 5). Nine cancer centers (but no pharmaceutical companies) submitted eight or more forms each.

### Coding Instrument

A coding instrument was developed to evaluate the content and tone of the consent forms. It included analysis of the presentation of the characteristics of the trial, the purpose and procedures of the research, benefits, risks, and alternatives. The instrument was pretested with coders to refine and clarify the questions. Nine persons coded the consent forms. Coders had at least a college education; six of the nine had no clinical experience. Each consent form was scored separately by two coders; a third coder adjudicated areas of disagreement.

Agreement was characterized as the same response from both graders; for items that were rated on a scale, agreement was characterized in point clusters or as a difference that did not exceed one point. For 81 percent of the questions not related to characteristics of the trial (21 of 26), there was greater than 80 percent agreement between coders, and for an additional 3 questions, there was between 75 and 80 percent agreement. For two questions, one evaluating a distinction between procedures for standard care from procedures for research and the other a judgment about the overall understandability of the consent form, there was 56.9 percent agreement and 68.9 percent agreement, respectively.

### Characteristics of the Trial

Experimental agents were classified according to their general biologic mechanism. Eighty trials testing a single chemotherapeutic agent in humans for the first time were labeled as "classic" phase 1 cancer trials. Eighty-two trials testing a combination of chemotherapeutic agents, at least one of which was approved by the Food and Drug Administration (FDA) for use in the particular type of tumor, were classified as "combination" trials. When identifiable, sponsorship was recorded as industry, government, or academic or other. For trials with multiple sponsors, trials with any industry backing were classified as industry-sponsored; trials with both government and academic funding were classified as government-sponsored. Using subjective criteria, coders rated consent forms for understandability on a five-point Likert scale, on which 1 represented "confusing" and 5 represented "understandable."

### Description of the Purpose and Procedures of the Research

The consent forms were also assessed for a description of the trial as research, mention of the purpose of the research, and dis-

tinguishing of research-related procedures from procedures for routine clinical care. Any description of procedures indicating that they were specifically for research purposes was recorded as making this distinction, except for boilerplate statements in the financial section of the form describing the assignment of costs on the basis of this distinction.

### Description of Benefits and Risks

We noted how the forms described the probability of harms and benefits and whether they discussed death and other possible risks, as well as cure and other possible benefits.

### Alternatives

Discussion of alternatives to participation in the trial, such as standard treatment, other research trials, no treatment, and supportive or palliative care, was recorded.

### Statistical Analysis

Data were entered into an Excel data base and analyzed with the use of SAS software (version 8.0). Chi-square tests were performed to detect significant ( $P < 0.01$ ) differences in content between the following groups of forms: forms for classic trials and all other consent forms; forms for classic trials and forms for combination trials; forms that used a format for consent documents that is recommended by the NCI and forms that did not; forms for industry-funded trials and forms for non-industry-funded trials; forms for trials involving subjects with metastatic or advanced tumors and forms for trials not involving such subjects; and forms from institutions with more than the median number (five) of consent forms in the data sample and forms from institutions with fewer consent forms in the sample. To evaluate the effect of institutional boilerplate or required language on the results of this analysis, we evaluated the distribution of each individual question according to institution. Institutions contributing five or fewer consent forms were grouped together. Distributions were evaluated with an exact chi-square test for clustering according to institution.

## RESULTS

### Diversity of Phase 1 Oncology Trials

Of all 272 consent forms, 162 (60 percent) were for trials of chemotherapeutic agents only; the remainder were for studies of biologic agents, vaccines, and other agents (Table 1). Of the 162 forms for chemotherapeutic trials, 80 (49 percent) were for classic trials — those involving the escalation of the dose of a single agent that had not previously been tested in humans. The rest were for combination chemotherapy trials, which evaluated either a new agent in combination with an approved agent or agents or a new combination of FDA-approved agents. Therefore, of all the consent forms for phase 1 oncology trials that we evaluated, 80 (29 percent) were for classic chemotherapy trials, 82 (30 percent) were for combination chemotherapy trials, and 110 (40 percent) were for trials of biologic or other noncytotoxic agents.

Of all the forms, only 44 (16 percent) used the format recommended by the NCI (Table 1), and these forms were longer than those that did not use the NCI format (median length, seven pages vs. six;  $P < 0.001$ ). More forms that followed the NCI format (36 of 44 [82 percent]) than forms that did not follow this for-

TABLE 1. CHARACTERISTICS OF PHASE 1 ONCOLOGY TRIALS.\*

CHARACTERISTIC	ALL TRIALS (N=272)	CHEMOTHERAPY TRIALS			OTHER TRIALS				
		TOTAL (N=162)	CLASSIC (N=80)	COMBINATION (N=82)	IMMUNOLOGIC AGENT (N=23)	ANTI- ANGIOGENESIS FACTOR (N=13)	RADIOACTIVE AGENT (N=4)	GENE TRANSFER (N=9)	MISCELLA- NEOUS (N=61)
Type of subjects (%)									
Adults	90	89	85	89	91	100	50	89	93
Children	7	9	14	5	4	0	50	0	2
Adults and children	3	2	1	2	4	0	0	11	5
Source of funding (%)†									
Industry	63	65	73	57	61	85	25	78	54
Government	21	23	24	23	17	15	75	0	21
Academic	12	7	3	11	17	0	0	22	25
Unspecified	5	5	1	9	4	0	0	0	0
Format									
No. of pages									
Mean	6	6	6	6	7	7	6	8	6
Range	3-13	3-11	3-11	3-11	4-10	3-9	3-13	4-10	3-10
NCI format (%)	16	17	13	21	4	8	25	33	18

\*Chemotherapy trials were classified in two categories: classic trials, which test a single agent for the first time in humans, and combination trials, which test a number of agents in combination, at least one of which is approved by the Food and Drug Administration for use in the particular type of tumor. NCI denotes National Cancer Institute. Because of rounding, not all percentages total 100.

†Trials often had multiple sources of funding. They were classified as industry-funded if they had any funding from industry; trials with government and academic funding were classified as government-funded trials.

mat (136 of 228 [60 percent]) were rated as “understandable” by coders ( $P=0.008$ ). No institution used the NCI format for all consent forms, and only one institution used this format for more than 75 percent of its forms.

#### Portrayal of the Trial as Research or Treatment

Of all consent forms, 268 (99 percent) contained an explicit statement indicating that the study was research. In 231 of these forms (86 percent), this statement was considered by the coders to be “prominent,” in that it appeared in the first paragraph, was easy to identify, and was repeated at least once. Of all forms, 249 (92 percent) indicated that safety testing was the goal of the research, and 17 (6 percent) stated explicitly that it was not the purpose or the expectation of the trial to be therapeutic. Overall, 115 forms (42 percent) made a distinction between procedures performed for research purposes and those performed for the purposes of clinical care. A total of 260 forms (96 percent) referred to the investigational agent as “treatment” or “therapy,” without including modifying words such as “experimental” or “research” (Table 2). There was no effect of institution on these characteristics of the consent forms, because almost every form prominently described the study as research and yet used the term “treatment” or “therapy.”

#### Promise of Benefit

The section on benefit was an average of 4 lines long (range, 0 to 14) (Table 3). As possible benefits,

14 forms (5 percent) mentioned cure, 53 (19 percent) mentioned prolongation of life, 96 (35 percent) mentioned tumor shrinkage, and 7 (3 percent) mentioned access to diagnostic tests. Potential benefit to society through generalizable knowledge was cited in 185 forms (68 percent). Only 1 of the 272 consent forms stated that subjects were “expected” to benefit; 11 forms (4 percent) stated with certainty that subjects would not benefit; 255 forms (94 percent) communicated uncertainty about benefit; and 5 forms (2 percent) said nothing about the chance of benefit. Yet 139 forms (51 percent) alluded to the possibility of benefit in a section other than the designated benefit section — usually in the statement of purpose — by including statements such as “some patients have benefited from treatment with this drug” or “this drug has shown some promise in this disease and has improved patients’ blood counts.” There was some clustering according to institution among forms that listed cure and prolongation of life as possible benefits. Cure was listed as a possible benefit only in forms from two institutions ( $P<0.001$  for the effect of institution), and prolongation of life was mentioned in more than one consent form from only three institutions ( $P<0.001$  for the effect of institution).

#### Warnings about Risks

The mean length of the section on risks was 35 lines (range, 5 to 147) (Table 3). Overall, 181 forms (67 percent) mentioned at least once that death could be caused by the experimental agent; 224 (82 per-

DESCRIPTIONS OF BENEFITS AND RISKS IN CONSENT FORMS

TABLE 2. DESCRIPTION OF RESEARCH PROVIDED IN CONSENT FORMS.\*

VARIABLE	ALL TRIALS (N=272)	CHEMOTHERAPY TRIALS		OTHER TRIALS (N=110)
		CLASSIC (N=80)	COMBINATION (N=82)	
		percent		
Statement that the study is research				
Explicit	99	99	98	99
Prominent†	86	82	89	86
Identification of trial as dose-escalation, safety, or toxicity study	92	96	91	90
Differentiation of research procedures from clinical care procedures‡	42	59	29	40
Reference to investigational agent as “treatment” or “therapy” without “experimental,” “investigational,” or “research” as modifier	96	100	95	93

\*Chemotherapy trials were classified in two categories: classic trials, which test a single agent for the first time in humans, and combination trials, which test a number of agents in combination, at least one of which is approved by the Food and Drug Administration for use in the particular type of tumor. Other trials include 23 trials of an immunologic agent, 13 trials of an antiangiogenesis factor, 4 trials of a radioactive agent, 9 trials of gene transfer, and 61 miscellaneous types of trials.

†A statement was considered to be prominent if it appeared in the first paragraph of the consent document, was easy to identify, and was repeated at least once.

‡P=0.002 for the comparison between classic and combination trials.

TABLE 3. DESCRIPTIONS OF RISKS AND BENEFITS IN CONSENT FORMS.\*

VARIABLE	ALL TRIALS (N=272)	CHEMOTHERAPY TRIALS		OTHER TRIALS (N=110)
		CLASSIC (N=80)	COMBINATION (N=82)	
<b>Risks section</b>				
Separately labeled section (%)	97	100	93	99
Length (lines)†				
Median	35	23	38	37
Range	5–147	6–75	6–140	5–147
Mention of possible risks (%)				
Death	67	65	67	67
Serious harms	82	81	87	81
Treatable harms	82	75	87	83
Unknown harms	84	85	87	82
<b>Benefits section</b>				
Separately labeled section (%)	96	98	93	98
Length (lines)				
Mean	4	4	4	4
Range	0–14	0–14	1–8	1–10
Mention of possible benefits (%)				
Cure	5	5	2	6
Tumor shrinkage	35	33	30	42
Prolongation of life	19	19	23	18
Claim of definite direct benefit (%)	<1	0	0	<1

\*Chemotherapy trials were classified in two categories: classic trials, which test a single agent for the first time in humans, and combination trials, which test a number of agents in combination, at least one of which is approved by the Food and Drug Administration for use in the particular type of tumor. Other trials include 23 trials of an immunologic agent, 13 trials of an antiangiogenesis factor, 4 trials of a radioactive agent, 9 trials of gene transfer, and 61 miscellaneous types of trials.

†P<0.001 for the comparison between classic and combination trials.

cent) identified some risks as severe, permanent, or both; and 222 (82 percent) labeled some risks as treatable, reversible, or both. Two hundred one forms (74 percent) estimated the probability of risks either quantitatively (with percentages, ratios, or both) or qualitatively (with terms such as “often” or “rare”); the other 71 forms did not estimate the probability of harms at all. Of all forms, 229 (84 percent) mentioned the possibility of unknown risk.

A total of 39 of the 44 forms that used the NCI format (89 percent) listed death as a possible risk, and 43 (98 percent) identified risks as severe. These rates were significantly higher than those among the 228 forms without the NCI format, 141 of which (62 percent) mentioned death as a possible risk ( $P < 0.001$  for the comparison with the forms with NCI format), and 182 of which (80 percent) identified risks as severe ( $P = 0.002$ ).

There was an effect of institution on the listing of the risk of death ( $P < 0.001$ ), since more than 80 percent of the forms from six institutions (only three of which used the NCI format for any of their forms) mentioned the possibility of death. Similarly, at these six institutions and four others, more than 80 percent of forms indicated that side effects could be serious or permanent ( $P = 0.002$ ).

#### Mention of Alternatives

Overall, 178 consent forms (65 percent) mentioned the alternative of receiving no treatment; 238 (88 percent) cited standard treatments, such as standard chemotherapy, surgery, radiation, or some combination of these treatments; and 142 (52 percent) referred to other experimental agents as alternatives to participation in the trial. Of all forms, 152 (56 percent) mentioned palliative or supportive care as an alternative, and 72 (26 percent) specified relief of symptoms as an alternative. Only 1 of 272 consent forms mentioned hospice care as an alternative (Table 4). Three of 272 forms did not mention the subject’s right to withdraw from the trial at any time.

Forms for trials involving subjects with metastatic or advanced cancers included other experimental therapies as alternatives more often (125 of 222 forms [56 percent]) than forms for trials that did not involve subjects with such cancers (17 of 49 [35 percent],  $P = 0.007$ ). Similarly, forms using the NCI format mentioned palliative care as an option more often (33 of 44 forms [75 percent]) than forms without this format (119 of 228 [52 percent],  $P = 0.008$ ). Palliative care was listed as an alternative in more than 80 percent of the consent forms from four institutions ( $P < 0.001$  for the effect of institution), and the alterna-

**TABLE 4.** MENTION IN CONSENT FORMS OF ALTERNATIVES TO PARTICIPATION IN THE TRIAL.\*

VARIABLE	ALL TRIALS (N=272)	CHEMOTHERAPY TRIALS		OTHER TRIALS (N=110)	TRIALS INCLUDING SUBJECTS WITH ADVANCED OR METASTATIC TUMORS (N=222)	TRIALS NOT INCLUDING SUBJECTS WITH ADVANCED OR METASTATIC TUMORS (N=49)
		CLASSIC (N=80)	COMBINATION (N=82)			
percent						
Separately labeled section on alternatives	96	96	90	99	95	98
Alternatives mentioned						
Palliative or supportive care†	56	69	62	42	58	45
Relief of symptoms‡	26	42	23	17	29	18
Hospice care	<1	0	1	0	<1	0
No treatment	65	68	70	61	67	61
Standard treatment	88	80	91	90	87	88
Other experimental therapies§	52	68	57	37	56	35

\*Chemotherapy trials were classified in two categories: classic trials, which test a single agent for the first time in humans, and combination trials, which test a number of agents in combination, at least one of which is approved by the Food and Drug Administration for use in the particular type of tumor. Other trials include 23 trials of an immunologic agent, 13 trials of an antiangiogenesis factor, 4 trials of a radioactive agent, 9 trials of gene transfer, and 61 miscellaneous types of trials.

† $P = 0.007$  for the comparison between classic chemotherapy trials and all other trials.

‡ $P < 0.001$  for the comparison between classic chemotherapy trials and all other trials.

§ $P = 0.001$  for the comparison between classic chemotherapy trials and all other trials;  $P = 0.007$  for the comparison between trials including subjects with advanced or metastatic tumors and trials not including such subjects.

tive of receiving no treatment was mentioned in more than 80 percent of forms from six institutions ( $P=0.006$  for the effect of institution).

#### Consent Forms for Classic Phase 1 Oncology Trials

Overall, consent forms for classic trials testing a single, previously untested chemotherapeutic agent were not significantly different from all other consent forms in terms of the risks and benefits mentioned (Tables 1, 2, 3, and 4). However, forms for classic trials distinguished between research-related procedures and procedures for clinical care more often than other forms (59 percent vs. 36 percent,  $P<0.001$ ). Consent forms for classic phase 1 trials also had significantly shorter sections addressing risks than forms for combination trials (median, 23 vs. 38 lines;  $P<0.001$ ). Forms for classic trials presented the alternative of palliative care significantly more often than all other forms (69 percent vs. 51 percent,  $P=0.007$ ); similarly, they were more likely to mention the relief of symptoms as an alternative (42 percent vs. 20 percent,  $P<0.001$ ) and to mention other experimental therapies as alternatives (68 percent vs. 46 percent,  $P=0.001$ ).

### DISCUSSION

Our results indicate that the majority of 272 consent forms used for phase 1 oncology trials in 1999 stated that the trial constituted research, did not promise benefit (and acknowledged the uncertainty of direct clinical benefit), and discussed risks extensively, frequently mentioning the possibility of death. Although the forms may need to do more to counteract inflated expectations of benefit, the impression that consent forms for phase 1 oncology trials distort the nature of research, overpromise benefits, especially cure, and downplay risks<sup>19</sup> is not supported by our data.

Almost all the forms we examined conveyed the fact that the study was research, and most disclosed that the purpose was to test the safety of an experimental regimen. However, fewer than half the forms distinguished research-related procedures from procedures for standard care, and nearly all repeatedly referred to the agent being studied as “treatment” without specifying that it was “experimental” or “investigational” treatment. We believe that the forms should have stated more explicitly that the agent was experimental and not a proven treatment, especially in dose-escalating chemotherapy trials.

More important, the consent forms contained detailed warnings about risks and did not overstate the prospect of benefit. As an indication of the emphasis on risks, the section of consent forms detailing risks was, on average, nearly 10 times as long as the section on benefits. In addition, two thirds of the forms warned of the possibility of death, while only 1 consent form stated that direct benefit to subjects was

“expected,” and only 5 percent mentioned cure as a possible benefit; on the other hand, only 11 forms explicitly said that benefit was unlikely. Together, these data demonstrate that consent forms discuss the seriousness and unpredictability of risk in phase 1 oncology research and rarely promise direct benefit.

Discussion of the alternatives to participation in the research, however, was more variable and less comprehensive. Although most consent forms mentioned standard treatment as an alternative, barely half included palliative care or other experimental regimens, and forms from certain institutions mentioned none of these alternatives. Only one consent form mentioned hospice care as an alternative.

The diversity of experimental agents and regimens we encountered in this study suggests that the risk-benefit profile of phase 1 oncology research is much more variable than is generally believed. Classic dose-escalating trials of untested chemotherapeutic agents offered to patients with a terminal illness who have exhausted most other options made up less than one third of the phase 1 oncology trials in the sample. Furthermore, the participation of subjects with nonadvanced cancers in 49 of the trials (18 percent) suggests that the alternatives to participation in research may vary depending on the population of subjects. This variability in risk, prospect of benefit, and alternatives suggests that disclosure should be tailored to the specifics of the trial in question.

The results of this study suggest four areas for improvement of consent forms for phase 1 oncology trials. First, forms should use terms such as “research drug or agent” to refer to the investigational agent, instead of simply “treatment,” which implies that an agent has some proven efficacy in treating the disease. Second, these forms, especially those for classic phase 1 trials, should always distinguish between procedures performed for research purposes and those related to standard care in a way that ensures that subjects understand the difference. Third, although only one consent form promised direct benefit, more forms should explicitly acknowledge that phase 1 trials are neither designed nor expected to provide direct benefits to subjects.<sup>30</sup> Finally, it is important that more consent forms provide a comprehensive discussion of available alternatives to participation in research.

There are several limitations to this study. First, the perspectives of the coders did not encompass the full range of perspectives of actual research subjects; six of the nine coders had no clinical experience, and all were college-educated. Second, our coding instrument may have failed to capture additional features that are important to the overall message conveyed. For instance, we did not specifically record whether consent forms listed “efficacy” among their research goals, a statement that could undermine the effective

communication of “safety testing” as the trial’s primary goal. Third, our data sample did not include consent forms for cancer trials conducted at non-NCI-designated cancer centers. Fourth, it is possible, though unlikely, that cancer centers selectively submitted some consent forms and not others, which would have produced a biased sample. Finally, variation in the accrual rate for each trial makes it likely that more subjects in phase I oncology trials received certain consent forms than received others.

In conclusion, consent forms for phase I oncology trials could do more to counteract misunderstandings that subjects may bring to a trial, but their substance does convey the purpose, risks, and benefits of the trials. Much of the attention currently devoted to consent forms by researchers, institutional review boards, and regulators could be directed more usefully to the enhancement of other aspects of the informed-consent process.

The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the Department of Health and Human Services or the National Institutes of Health.

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