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Evaluating the Quality of Information about Alternatives to Research Participation in Oncology Consent Forms

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Abstract

A careful consideration of the alternatives to research participation is an essential element of making an informed choice to enroll in a biomedical research study. While there is general agreement on the importance of informing prospective subjects about alternatives to research participation, little is known about how investigators communicate this information. The purpose of this study was to attempt to assess the quality of information about alternatives contained in informed consent documents in oncology randomized controlled trials. Our study indicates that there is room for improvement concerning the discussion of alternatives to research participation in informed consent documents in oncology randomized controlled trials. Though most of the documents in our study met the minimal disclosure standard found in the U.S. federal regulations, less than a third met the reasonable person standard, a widely accepted principle endorsed by the common law and various ethics guidelines and documents. There was a statistically significant difference between the alternative discussions in local and model forms ($P < 0.0014$). The alternatives discussions in local informed consent documents were more likely to receive higher scores than those in model consent documents, with an odds-ratio of 3.5 to 1.

Keywords

Informed consent; alternatives; regulation; ethics; oncology

Background

A careful consideration of the alternatives to research participation is an essential element of making an informed choice to enroll in a biomedical research study.[1] Many regulations and guidelines hold that investigators should provide prospective research subjects with information about alternatives. U.S. federal research regulations require that the informed consent process include “disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.”[2] The Council for the

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International Organizations of Medical Sciences (CIOMS) guidelines state that investigators should inform subjects about “any currently available alternative interventions or courses of treatment”. [3] It is especially important for investigators to discuss alternatives when prospective subjects have several treatment options for their medical condition, some of which may be preferable to participating in a research study. [4]

While there is general agreement on the importance of informing prospective subjects about alternatives to research participation, little is known about how investigators communicate this information. While many studies have been conducted on informed consent in research, few of these examine the discussion of alternatives. [5] In 2003, Horng et al published a study on informed consent documents in Phase I oncology studies that included some data on the description of alternatives to research participation. They found that 88% of the consent forms mentioned standard treatments as alternatives to research participation, 65% mentioned the option of receiving no treatment, 56% mentioned palliative or supportive care, and 52% mentioned other experimental treatments. [6] This study provided some useful data about the content of information contained in oncology consent forms, but it did not attempt to assess the quality of that information.

A more recent study conducted by two of us (and three other authors) suggested that there may be some cause for concern about the quality of alternatives discussions in informed consent documents. We found that only 17.4% of consent forms for oncology randomized controlled trials (RCTs) in which all of the treatments being investigated were available to the subjects without participating in the study actually informed subjects that they could receive these treatments off-study. [7] Information about the option of obtaining a treatment off-study is important for making a well-reasoned decision to participate in an RCT. [4] The purpose of our present study was to attempt to assess the quality of information about alternatives contained in informed consent documents in oncology RCTs.

Materials and Methods

The consent forms were drawn from the sample used in our previous study of alternatives, which was obtained by requesting consent forms from Phase II, III, or IV non-pediatric U.S. oncology RCTs registered in Clinicaltrials.gov, a clinical trials registry supported by the National Institutes of Health (NIH) containing over 75,000 studies. [4] Studies registered at this website are sponsored by government agencies, private industry, and private foundations and take place in all 50 states and 140 countries. Our initial search on Clinicaltrials.gov yielded 1794 studies that met our search criteria. This list was pared down to 749 studies in which all of the treatments were commercially available at the initiation of the study and there were no placebo control groups. We did not include RCTs that examined the effectiveness of surgical procedures or radiation therapy. Consent forms were requested from a random sample of 250 of these studies, and 104 consent forms were acquired. The NIH Office of Human Subjects Research determined that the federal regulations for protection of human subject did not apply to our study because we did not obtain private information about human subjects or interact with human subjects.

We developed a scoring system to measure the quality of the alternatives discussion and coded all of the consent documents using this system. The system is based on (1) the U.S. federal regulations, and (2) the reasonable person standard. The U.S. federal regulations mention 14 different types of information that investigators should disclose to subjects (where appropriate), including alternative procedures or courses of treatment. While this list is useful, it omits important types of information that most people would want to know, such as financial interests related to the research [9] and the disposition of biological samples. [10]

A widely recognized principle for disclosure that goes beyond the minimum regulatory requirements is the reasonable person standard, which has been adopted by most states in the U.S. and has been mentioned in various ethical guidelines, such as the Belmont Report.[1, 11] According to the reasonable person standard, physician/investigators should disclose information that a reasonable person would want to know to make an intelligent choice.[1,4] A strong argument can be made that a reasonable person would want to know something about the different alternatives in order to decide whether to choose one of the alternatives or participate in research, because to make an intelligent choice one must be able to evaluate the different options.[4,12] Simply knowing what the alternatives are does not necessarily help one decide whether to choose any of the alternatives.

With these two different legal standards in mind, we defined the scores as follows (see Table 1). We gave a consent form a score of “0” if it contained no discussion of alternatives; a “1” if it mentioned that alternatives exist but did not list or describe any alternatives; a “2” if it listed or described alternatives; and a “3” if it listed or described alternatives and provided some information that could be helpful in deciding whether to choose one of the alternatives, such as (a) potential benefits or risks of alternatives, (b) availability of alternatives, or (c) the nature of the alternatives, such as the procedures used, etc. Consent forms that scored a 0 did not even meet the minimum regulatory requirements, while forms with a score of 1 possibly met the regulatory requirements, depending on how “disclosure” is interpreted. Forms with a score of 2 or above met the regulatory requirements, and forms with a score of 3 met the regulatory requirements and the reasonable person standard. Two of us, DR and DP, independently scored all of the documents according to the measures we developed. DR and DP agreed on the initial coding of over 95% of the documents and resolved disagreements following further discussion.

In addition to rating the quality of the alternatives discussion, we also counted the number of words in the alternatives discussion and the number of words in the entire consent document, which gave a measure of the percentage of the document devoted to the discussion of alternatives. In counting the number of words in the alternatives discussion, we did not include some statements that were placed in the section marked “alternatives” (or some similar marking) which did not have anything to do with alternatives, such as statements informing subjects that they have a right to withdraw at any time or statements about compensation for research injuries or liability.

We also collected information on the age of the consent document, which was based on the approval date for document; source of funding for the study (private vs. public); and the type of consent document, i.e. model vs. local. A local form was defined as a form approved by a particular IRB, while a model form was defined as a document drafted by a committee, such as an Oncology Cooperative Group, which could be implemented at different sites and approved by local IRBs. We were able to identify model forms because we requested them from Oncology Cooperative Groups. Most local forms included information, such as an approval date, that indicated a particular local IRB had approved the document.

We analyzed the alternative discussion scores for each consent document as an ordered categorical variable, taking ordinal values of 0 (lowest), 1, 2, 3 (highest). Using this ordinal response variable, we compared various factors, such as, (a) type of form (model versus local), (b) source of funding (private or public), (c) percentage of the words in the document devoted to the alternatives discussion, and (d) age of the form. We performed ordinal regression analysis using PROC GENMOD available in the statistical software package SAS (version 9.1).

Results

57.7% of informed consent documents scored a 2 for their discussion of alternatives, 32.7% scored a 3, 4.8% scored a 1, and 4.8% scored a 0. 52.9% of the documents were model forms and 47.1% were local. 53.8% of the studies were publicly funded, and 46.2% were privately funded. The average age of the consent forms was 2.4 years (i.e. beginning of 2005), and the average percentage of the document devoted to the discussion of alternatives was 2.4%.

Our most significant finding is that less than a third of the documents scored a 3 and nearly one tenth of the documents did not even score a 2. In other words, more than two thirds of the documents did not meet the reasonable person standard for disclosure, and nearly one tenth of the document may not have met the regulatory requirements. Table 2 includes samples of different scores.

Another important finding is that there was a statistically significant difference between the alternative discussions in local and model forms ($P < 0.0014$). Local informed consent documents were more likely to receive higher scores for alternatives discussions than model consent documents, with an odds-ratio of 3.5 to 1. This result was surprising, since we did not expect to see this type of difference between model and local forms because the same regulations and provide guidance for IRBs and committees that draft consent forms. One possible explanation for this result is that IRBs may appeal to different (i.e. higher) standards for informed consent than research committees that develop informed consent documents for multisite clinical trials. Another possible explanation is that IRBs may have access to information about the local availability of alternatives that committees that draft consent forms lack. The difference between the alternative discussions in model and local forms can be explained by a higher percentage of local forms that scored a 3 compared to model forms. 41.5% of local forms scored a 3 as compared to 23.5% of model forms.

An interesting finding is that forms containing a higher percentage of words devoted to the alternatives discussion were more likely to receive higher scores ($P < 0.0001$). The odds ratio was 2.06 to 1 that the score of the form would be higher for every 1% increase in the percentage of words devoted to the discussion of alternatives. One would expect that these two variables would be associated, since the number of words used to describe something can be taken as an indicator of the amount of information conveyed. However, we did find that some of the consent documents bucked this trend by using a lot of words to say very little.

None of the other variables were significant at $P < 0.05$. For example, the difference between public and private sponsors was not significant ($P < 0.2786$) and similarly, the age of the form was not significant ($P < 0.8261$).

Discussion

Our study indicates that there is room for improvement concerning the discussion of alternatives to research participation in informed consent documents in oncology RCTs. Though most of the documents in our study met the minimal disclosure standard found in the U.S. federal regulations, less than a third met the reasonable person standard, a widely accepted principle endorsed by the common law and various ethics guidelines and documents. As noted earlier, very little research has been conducted on the discussion of alternatives informed consent. Our study suggests there is a need for additional research to better understand how investigators communicate information about alternatives to research subjects and how this communication can be improved.

One reason why disclosure of alternatives in consent forms is often deficient is that these documents already contain so much information that there is not enough space to include a

more lengthy discussion of alternatives. Consent forms typically include an extensive discussion of the risks of various medications and treatments and detailed descriptions of the methods, procedures, and tests required by the study.[7] Including a comprehensive discussion of alternatives could significantly increase the length of consent documents, which frequently run to more than ten pages.[7] While we recognize the space constraints inherent in consent forms, we think there should be enough room for a better discussion of alternatives than found in many of the documents we examined. There are other ways of economizing space in consent forms other than omitting important information that subjects need to decide whether to participate. For example, discussions of risks can be condensed in many cases.[4]

Our study has a few limitations. First, our results may not generalize to all clinical research, because our sampling frame was limited to consent documents in oncology RCTs conducted in the U.S. It is possible that sampling different types of consent documents would yield different results. There are reasons to believe, however, that consent documents in other types of clinical research conducted in the U.S. are not very different from the consent documents that we studied, since the same laws, regulations, and ethical norms would apply. It would be useful, however, to extend our study and determine whether similar results are obtained in other clinical research fields.

Second, our sample size (104) is relatively small. Though we do not believe that the small sample size had a dramatic impact on our results, we recognize that it is possible that a larger sample might yield different results. We would welcome additional studies that attempt to replicate our results.

Third, since our study examined consent forms, not the entire process of consent, it is possible that investigators may communicate information to subjects about alternatives to research participation that is not contained in the consent form. The consent form is but one part of the process of consent, which also includes candid discussions between investigators and research subjects. We acknowledge that this is an important limitation of our study, and for that reason we recommend that additional research be undertaken to examine other parts of the process of consent. For example, studies could interview subjects and investigators concerning discussions of alternatives to research. Other studies could observe investigator-subject interactions.

While we acknowledge the possibility that investigators may convey information about alternatives to subjects during the consent process that is not contained in the consent document, we do not expect that this is often the case, because there is so much information to discuss during the consent process other than alternatives, such as the nature of the research, risks and benefits, etc.[1] Moreover, even though the consent document is only part of the process of consent, it is still important to ensure that the document contains important information that subjects may need for decision-making, since subjects may forget information conveyed during conversations with investigators and IRBs have no oversight over these informal discussions. [13] Since most IRBs do not routinely observe the process of consent, the IRB's primary method for ensuring that subjects receive information they need to know is to require that the information be included in the consent document. The review of consent documents is therefore a crucial part of the oversight of research with human subjects.[13]

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References

1. Berg, J.; Appelbaum, P.; Parker, L.; Lidz, C. Informed consent. 2. New York: Oxford University Press; 2001.
2. 45 CFR 46.116a4 (2005); see also 21 CFR 50.25a4 (2008).
3. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects. [Accessed: June 25, 2009]. Available at: http://www.cioms.ch/frame_guidelines_nov_2002.htm
4. Menikoff, J. What the doctor didn't say. New York: Oxford University Press; 2007.
5. Flory, J.; Wendler, D.; Emanuel, E. Empirical issues in informed consent research. In: Emanuel, E.; Grady, C.; Crouch, R.; Lie, R.; Miller, F.; Wendler, D., editors. The Oxford textbook of clinical research ethics. New York: Oxford University Press; 2008. p. 645-60.
6. Horng S, Emanuel E, Wilfond B, Rackoff J, Martz K, Grady C. Descriptions of benefits and risks in consent forms for phase 1 oncology trials. *N Engl J Med* 2002;347:2134–40. [PubMed: 12501226]
7. Resnik D, Peddada S, Altilio J, Wang N, Menikoff J. Oncology consent forms: failure to disclose off-site treatment availability. *IRB* 2008;30(6):7–11. [PubMed: 19119758]
8. Capron, M. Legal and regulatory standards of informed consent in research. In: Emanuel, E.; Grady, C.; Crouch, R.; Lie, R.; Miller, F.; Wendler, D., editors. The Oxford textbook of clinical research ethics. New York: Oxford University Press; 2008. p. 613-32.
9. Kim S, Millard R, Nisbet P, Cox C, Caine E. Potential research participants' views regarding researcher and institutional financial conflicts of interest. *J Med Ethics* 2004;30:73–9. [PubMed: 14872080]
10. Hull S, Sharp R, Botkin J, Brown M, Hughes M, Sugarman J, Schwinn D, Sankar P, Bolcic-Jankovic D, Clarridge B, Wilfond B. Patients' views on identifiability of samples and informed consent for genetic research. *Am J Bioeth* 2008;8(10):62–70. [PubMed: 19003716]
11. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Washington, DC: Department of Health, Education and Welfare; 1979 [Accessed: July 2, 2009]. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Available at: <http://ohsr.od.nih.gov/guidelines/belmont.html#goc1>
12. Resnik, D. Choices: an introduction to decision theory. Minneapolis: University of Minnesota Press; 1987.
13. Resnik D. Do informed consent documents matter? *Contemp Clin Trials* 2009;30:114–5. [PubMed: 18977313]

Table 1

Scoring system for alternatives discussions

Score	Definition
0	Document does not include a discussion of alternatives
1	Document mentions that alternatives exist but does not list or describe Alternatives
2	Document lists or describes alternatives
3	Document lists or describes alternatives and provides information that could be useful in deciding whether to choose any of the alternatives

Table 2**Examples of Different Scores for Alternatives Discussions**

Score	Example
0	(No discussion of alternatives)
1	<p>Alternatives: Your other choice is not to take part in this study, and your physician will discuss this with you.</p>
2	<p>What Other Options Are There? You can receive treatment for non-small cell lung cancer without being on this study. Instead of participating in this study, you have these options:</p> <ul style="list-style-type: none"> • Supportive care only to treat symptoms. • Chemotherapy only, such as docetaxel, without the addition of cetuximab or bortezomib <p>Please talk to your doctor about these and other options.</p>
3	<p>ALTERNATIVE APPROACHES OR TREATMENTS It should be emphasized that we do not know at this point whether VELCADE combined with EPOCH-R with or without maintenance VELCADE is superior, inferior, or equivalent to standard combination chemotherapy for your disease. Alternative procedures that could be used to treat your disease include: Other combination drug regimens and other schedules of the same drugs used in this study. For example, a chemotherapy called CHOP given in the conventional manner would be suitable standard therapy for your condition. You could also receive CHOP-R or EPOCH-R as standard treatment.</p> <ul style="list-style-type: none"> • Treatment with single drugs. This is known to produce brief responses of a few months' duration in many patients but to have little beneficial effect in long-term control of the disease. • Radiation (X-ray) treatments. This can stop tumor growth in particular locations, such as bone, abdomen, and other sites but is not successful in controlling the disease overall unless the disease is very localized at the start of therapy. • Surgery. As with radiation, surgery can be successful in removing tumor from particular locations but cannot be used successfully to remove all lymphoma cells from the body, since the disease is almost always present in multiple locations. Also, surgery cannot be used against tumor in some of the organs most commonly involved by lymphoma, such as the liver or the lungs. • Watching and waiting may be an option for select patients without symptoms.