Informed Consent in Clinical Trials: Will the Proposed Changes to the Common Rule Address Current Criticisms?

By Andrew Rusczek

Despite decades of human subjects protection regulation, training and oversight, overwhelming evidence demonstrates that clinical trial subjects often fail to understand even the most fundamental aspects of the clinical trials in which they participate, such as the risks of participation, how subjects are randomized into different treatment arms, and the differences between treatment and clinical research. This lack of understanding undermines the ethical foundations of clinical trials.

On July 26, 2011, the Secretary of the U.S. Department of Health and Human Services (HHS) proposed changes to the Common Rule in an Advance Notice of Proposed Rulemaking (ANPRM). The proposed changes related to informed consent, however, do not fully address the problem of subject comprehension and may even exacerbate it.

Section 1, below, outlines the ethical foundations of informed consent in clinical trials. Section 2 discusses criticisms of the current informed consent process in clinical trials and, in particular, informed consent forms (ICFs). Section 3 highlights HHS’s proposed changes to ICFs and discusses the extent to which these proposed changes may address criticisms. Section 4 concludes.

1. Ethical Foundations of Informed Consent in Clinical Trials

Except in very limited circumstances, informed consent is a crucial component of an ethical clinical trial. Informed consent is founded on the principle of respect for autonomy, which holds that people have the capacity to govern themselves and that this capacity should be respected. Informed consent is especially important in the clinical trial context (as compared to the therapeutic treatment context) because clinical trial subjects put themselves at risk of harm at least in part to benefit society.

Informed consent is designed to provide subjects control over whether to participate in a trial based on their preferences and values. Informed consent operates in three steps: the subject’s receipt of information, the subject’s understanding of this information, and the subject’s independent and voluntary consent to participate.

Before a subject can make an informed decision whether to participate in a trial, the subject must receive truthful information pertinent to the subject’s decision, including information about the purpose of the trial, the trial procedures, alternative treatments available for the subject’s medical condition (if the trial involves therapy), and potential risks and benefits of participating in the trial.

The subject benefits from receiving this information only to the extent that the subject understands the information provided. The information must therefore be presented in a manner that facilitates the subject’s understanding, given the subject’s education, cognitive skills, language and background. The researcher should avoid technical and legal language that may be unfamiliar to the subject. The subject’s understanding may also be impeded if the information is presented in a hurried manner or if the subject does not have adequate time to consider the information. The researcher also should strike a balance between providing the subject enough information to make an informed decision but not so much
information that the subject loses interest or the information most relevant to the subject’s decision is obscured.⁸

Once the subject receives and understands relevant information about the trial, the subject’s consent to participate in the trial must be wholly voluntary. The subject’s consent must be free from undue influence, coercion, manipulation or deception. For example, payment to a subject for participating in a clinical trial may constitute undue influence. While a signed ICF memorializes the subject’s consent to participate in a trial, the ICF is obviously of little value from an ethical perspective if the subject’s consent is based on incomplete information or understanding.⁹

2. Criticisms of Informed Consent in Clinical Research

Numerous studies show that the current informed consent process results in subjects’ inadequate understanding of even basic aspects of the clinical trials in which they participate.¹⁰ These concerns are heightened in the clinical research context because a patient may agree to participate in a trial for altruistic reasons, even though it is not in his or her best medical health interests.¹¹

For example, a number of studies show that the prevalence of “therapeutic misconception” in clinical trials may be due in part to defects in the informed consent process.¹² The term “therapeutic misconception” refers to a subject’s failure to understand that participating in a clinical trial requires some sacrifice of personal medical care. Subjects with a therapeutic misconception may overestimate the benefits or underestimate the risks of participating in a clinical trial, lack understanding of how subjects are randomized into different treatment arms, or fail to differentiate between treatment and clinical research.¹³ A subject with a therapeutic misconception, for example, may believe that the investigator will assign the subject to the study drug arm or placebo arm of the clinical trial based on that subject’s particular medical needs.

An analysis of 225 subjects from 44 clinical trials at two academic medical centers found that 62% of the subjects had a therapeutic misconception about the trial in which they participated.¹⁴ Another study of 207 subjects in cancer clinical trials found that a significant number of subjects had misunderstandings that could be characterized as therapeutic misconception.¹⁵ For example, approximately 30% of the subjects in this study falsely believed that the treatment under investigation had been proven to be the best treatment available for the subject’s type of cancer.¹⁶

Informed consent is a process, not a document. Nevertheless, the ICF is a vital part of the process. Three common criticisms of ICFs follow.

A. ICFs Are Too Long

One common criticism of ICFs is that they are too long.¹⁷ For example, one study found that consent documents for oncology trials conducted at the Emory University Winship Cancer Institute ranged from approximately four pages to 26 pages in length, with an average length of approximately 11 pages.¹⁸ A high school graduate with an average reading level would likely require 15 to 30 minutes to read an ICF of 11 pages, including time to re-read and review important provisions.¹⁹

The length of ICFs is concerning because, as the length of an ICF and the time it takes to read the ICF increase, it becomes less likely that subjects will read the entire ICF.²⁰ Given that research has shown that people are unlikely to read documents over four pages long and that often insufficient time is allocated to the consent process,²¹ it is reasonable to conclude that many subjects will not closely read ICFs that are 11 pages long. Subject comprehension also has been shown to be related inversely to the length of the ICF.²²
In this study at Emory University Winship Cancer Institute, half of the ICFs were longer than 11 pages. Of course, in many Phase II and III trials, the researchers would be delighted if the ICF were only 11 pages long.

B. ICFs Are Hard to Read

ICFs are also criticized for being hard to read. The general consensus in the research community is that ICFs should be written at or below an eighth-grade reading level. Nevertheless, studies show that ICFs rarely meet this standard. For example, the above-mentioned study found that approximately 90% of the ICFs were written at or above a tenth-grade reading level. A separate analysis of informed consent documents from 114 U.S. medical schools found that the average readability grade level for the documents was 10.6. Readability assessments are based on data like the average number of syllables per word and the average number of words per sentence.

C. ICFs Are Designed Primarily to Provide Legal Protection

Another criticism of ICFs is that they are primarily designed to provide legal protection to the institution, investigator and sponsor, rather than to provide useful information to the study subject for informed consent purposes. The ICF’s role as legal protection is likely one reason many ICFs are too long and too hard to read.

In a subject injury lawsuit, the ICF would be a key issue. The defendant would argue that the ICF was adequate, and the plaintiff would argue that it was not. The plaintiff would be likely to assert that the ICF failed to make certain disclosures (e.g., failed to fully and accurately disclose the possibility of the plaintiff’s injury). The plaintiff could also assert that a long, densely written ICF filled with legalese did not provide information in a form conducive to the plaintiff’s understanding and informed consent.

D. Other Criticisms of Informed Consent

There appear to be an endless number of criticisms of ICFs and the informed consent system more generally. For example, some argue that many ICFs are designed by institutions and sponsors as sales documents for the clinical trial. These ICFs appear to be drafted to minimize risks or highlight remote potential benefits. Others argue that researchers often fail to obtain subject consent before trial procedures begin; subjects are exposed to informal persuasion by researchers or the institution; subjects are not re-consented when changes are made to the protocol or new information becomes available; and ICFs fail to include important information.

3. ANPRM’s Proposed Changes to Requirements for Informed Consent

On July 26, 2011, HHS, through an ANPRM, requested comments on how the Common Rule could be modernized to better protect human subjects. In the ANPRM, HHS proposed revising informed consent requirements in the Common Rule to address criticisms that ICFs are too long and hard to read, are drafted to protect institutions rather than to facilitate subject informed consent, are intended as sales documents for clinical trials, and fail to include important information. To address these and other criticisms of ICFs, HHS proposed the following changes to the informed consent requirements in the Common Rule:

- Prescribe appropriate content for ICFs with greater specificity than in current Common Rule requirements.
- Restrict content inappropriate for ICFs.
- Limit length of various sections of ICFs.
Prescribe how information should be presented in ICFs (e.g., specifying information that should be included at the very beginning or specifying types of information that should be included in appendices rather than in the main body).

Reduce “boilerplate” language in ICFs that is intended to protect institutions from lawsuits rather than genuinely inform subjects.

Make available standardized ICF templates that meet regulatory requirements.

The proposed changes, however, are limited to the ICF and do not address the informed consent process more broadly, as noted by the Secretary’s Advisory Committee on Human Research Protections in its recommendations to HHS on the ANPRM. If informed consent is, in fact, a process and not just a document, the process should receive some attention in the revised regulations. Although one of the most effective means of improving subjects’ understanding is for investigators to devote more time to speaking with them one-on-one about the clinical trial, the proposed changes in the ANPRM do nothing to incentivize such communications.

The proposed changes also do not directly address the legitimate view that the ICF serves a crucial role in the defense of a subject injury lawsuit. Without any regulatory protection, institutions and sponsors will continue to have a legal incentive to pack information into the ICF, especially information regarding the potential risks of participating in a clinical trial.

Likewise, while the proposed limitation on the length of various sections of ICFs would help reduce the overall length of ICFs, this proposed limitation has been criticized as inappropriately limiting the right of an IRB to address issues in the ICF as it deems appropriate. Certainly, regulatory requirements to include items that might be irrelevant or inconsequential in a specific study could be eliminated. Given the wide variety of clinical trials, however, it is unclear how regulations could be drafted for eliminating text more broadly without affecting the rights of investigators, institutions, sponsors and subjects.

Reorganizing ICFs to focus on the most important points may be a more promising approach.

4. Conclusion

The clinical research enterprise has clearly not created a system that consistently obtains truly informed consent from study subjects. This is not to say that failure is inevitable, only that there are ample opportunities for improvement. While the changes proposed in the ANPRM will, to some extent, address common criticisms of ICFs, these changes are unlikely to be sufficient by themselves. It is therefore the responsibility of investigators, institutions, IRBs and sponsors to review their own ICFs and informed consent processes to improve performance against ethical and regulatory requirements for truly informed consent.

References
4. See id. at 696.
5. See Emanuel, supra note 2, at 2706.
PROTECTION OF HUMAN SUBJECTS OF RESEARCH 10-14 (1974) [hereinafter BELMONT REPORT]; Moreno, supra note 3, at 691; Emanuel, supra note 2, at 2706-07.

7. See BELMONT REPORT, supra note 6, at 11.
8. See id. at 12; Moreno, supra note 3, at 691.
9. See BELMONT REPORT, supra note 6, at 12; Moreno, supra note 3, at 691.
11. See Emanuel, supra note 2, at 2706. Due in part to these heightened concerns for clinical trials, informed consent in the clinical trial context is more closely regulated and enforced than informed consent in the therapeutic treatment context. See Moreno, supra note 3.
13. See id.
14. See id. at 1, 3, 5.
16. See id. at 1772, 1775.
18. See Sharp, Oncology Trials, supra note 17.
19. See id. at 573; Norman M. Goldfarb, Readable Informed Consent Forms Are Not Optional, 1 J. CLINICAL RES. BEST PRACT. 9, 1 (2005) [hereinafter Goldfarb].
20. See Sharp, Oncology Trials, supra note 17, at 572-73; Goldfarb, supra note 19, at 1.
21. See Sharp, Oncology Trials, supra note 17, at 573; Goldfarb, supra note 19, at 1-2.
25. See Sharp, Oncology Trials, supra note 17.
27. See, e.g., Albala, supra note 17; Goldfarb, supra note 19, at 2-3; Sharp, Oncology Trials, supra note 17, at 573.
28. See, e.g., Albala, supra note 17, at 3; Goldfarb, supra note 19, at 2-3; Sharp, Oncology Trials, supra note 17, at 573.

30. See, e.g., Sharp, Common Problems, supra note 22, at 134.


33. See id. at 44513.

34. Letter from Secretary’s Advisory Committee on Human Research Protections to Kathleen Sebelius, Secretary of HHS, 14 (Oct. 13, 2011) [hereinafter SACHRP].


36. See SACHRP, supra note 34, at 15.

37. See id.

38. See id.

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