

Opportunities to Improve Informed Consent

Frequently Observed Problems in Processes and Content

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Improving the informed consent process and consent forms can not only help subjects better understand clinical research but also reduce the number of invalid consents obtained.

“Full disclosure is a necessary precondition to free choice. Accordingly, subjects who do not understand the potential risks of a trial cannot be said to have chosen freely to face those risks.”
—Donna Shalala, PhD¹

There continues to be much interest in informed consent, both its theoretical underpinnings and its practical applications. As clinical auditors who have reviewed hundreds of consents at clinical research sites and asked staff members about their consenting procedures, we observe, first-hand, some of the practical applications of sponsor, CRO, and investigator attempts to adhere to good clinical practice standards and guidelines for informed consents. Despite widespread attention to tightening this component of clinical research, there remains much room for improvement.

Federal regulation and industry standards regarding informed consent have shifted progressively over time. Kiev, in a comprehensive review of the informed consent doctrine and its application to clinical research, discusses the evolu-

tion of case and administrative law leading to greater patient self-determination and rational decision-making.² It is now expected that potential subjects be provided with disclosure of facts, probabilities, and opinions material to their making an intelligent choice or decision about participating in a clinical study. Some recent civil cases, in which investigator conflict of interest and breach of fiduciary duty resulted in a failure to disclose an important material fact, have resulted in the necessity for even more disclosure of information.

Readability. Interest in improving the readability of informed consents is growing. Zaneccchia³ and Hochhauser⁴ examined readability issues and devised strategies to make consents more comprehensible. In general, these strategies aim at simplification, completeness, and improved visual appeal.

In 2000, Hochhauser⁵ reviewed 12 randomly selected consent forms submitted to a hospital institutional review board. He determined that they were difficult to read. They had too many uncommon words, too many words per sentence, and sometimes failed to meet good document design principles. In 1998 the National Cancer Institute published guidelines that would facilitate development of easy-to-read consent forms.⁶ As Hochhauser, who used these guidelines in his analyses, points out, “Word familiarity has been shown to be a major factor in a reader’s ability to understand written materials. Prospective participants have a hard time understanding not only words but basic clinical research concepts as well.”

Lin and a team of reviewers assessed consent forms for 71 studies conducted in Taiwan.⁷ The four most frequent defi-

TABLE 1 Problems with content and readability

Content Problem	Comments
No mention of informing subject's primary care MD regarding enrollment in the study.	An ICH recommendation; subject should grant permission to contact primary MD.
Title is not exact title on protocol.	Perhaps an attempt by study staff to make the consent title more understandable.
No mention of sponsor by name.	Investigator does not want the subject to know that the study is sponsored by a pharmaceutical company.
Inadequate discussion of compensation for injury and who will cover these costs (errors and omissions insurance purchased by the sponsor).	Happens frequently. The wording is confusing and often discusses subject's health insurance.
No IRB or patient advocate contact listed (name and title).	IRB does not want this person named.
Unclear regarding length of time subject will be on study (length of commitment); little mention of the amount of follow-up required.	Consent is vague regarding how many weeks, months, or years a subject will have to be followed after receiving drug.
Risks do not match investigator drug brochure; risks downplayed.	Investigator does not want to frighten away potential subjects.
No statement of subject payment in benefits or cost reimbursement section.	Dollar payments for travel, day care, completing study visits, etc. are not listed.
No mention of follow-up of pregnancy to term; use of adequate birth control.	Many investigational drugs are too risky to try on pregnant women, but the consent does not strongly state a woman must use birth control while on study and does not indicate what happens should she become pregnant.
No mention of possible pain associated with procedures, such as blood draws or mammograms.	Frequently downplayed.
Unclear about percentage chance of receiving study product (flip of coin).	Needs to be carefully explained, given the study arms and given the potential for harm (going untreated or undiagnosed) of receiving a placebo.
No mention of consequences of receiving the placebo and going untreated or undiagnosed.	Subjects need to understand natural disease progression and its risks.
No mention of access to medical records should subject be hospitalized or receive care at non-study health care facilities.	Especially important with the implementation of HIPPA legislation on 14 April 2003.
Alternative treatment risks and benefits not described.	Sometimes this is only done orally by a physician during a "recruitment" discussion.
No mention of subject's responsibility of to inform site staff about pregnancy, and new addresses and phone numbers.	Subjects have more than just a responsibility to present themselves for visits and submit to adverse events, procedures.
Amount of blood to be collected not specified in lay terms (teaspoons of blood).	Blood draws for lab testing are specified for many studies; their frequency and the amount of blood at each draw and total amount must be specified.
Confidentiality section only mentions that sponsor employees and FDA may review medical records; fails to mention sponsor representatives and EMEA.	CRO monitors, independent auditors, and other agency inspectors may be involved in record review.
Not updated with new safety information.	This is a GCP requirement, but like many requirements, it is difficult to determine when it is "triggered."
Number of study participants not specified.	Provides an understanding of how many subjects will be exposed.
Readability Problem	
Poor layout—no subheadings, text too dense.	Layout can be a formidable obstacle to comprehension.
Repetitious.	Unless the topic is extremely important; it should not be repeated.
Too wordy, too long, too many complicated terms, and/or does not follow a logical sequence in describing what will happen while on study.	Readers better comprehend short sentences, logically organized.
Content does not have changes recommended by the IRB.	IRBs usually have good reasons for requesting changes and these requests must be honored.
Missing signature lines for staff member administering consent, subject, and witness (if subject is "compromised").	Lines for signatures and dates help complete the process.
Absence of a line for time of day of consent (especially useful when consent is signed the same day that dosing or study procedures begin).	This line helps establish that consent was signed before study tests and procedures were initiated.
Confuses study MD with primarycare MD by using terms such as, "your physician."	It should be clear who is who.

TABLE 2 Problems with consent process

Problem	Comment
Not documented in a progress note.	A brief entry with date and time, acknowledging subject's comprehension of consent form and willingness to participate strengthens the process.
Impossible to tell whether consent process took place before or after study tests and procedures; process definitely occurred after study tests, dosing.	The consent document should note the time consent was obtained. All study-related tests that would not ordinarily be conducted must be performed after consent.
No MD involvement (in a complex study); consentor had inadequate clinical knowledge to adequately obtain subject's consent.	Some studies are so complex that they require substantial physician involvement. Consentors must have the requisite clinical background to administer consent; medical assistants typically do not.
Consent form signed by consenting clinician and subject on different dates.	Consent must be signed and dated when it is obtained. Different dates suggest that maybe the "named" consentor was not the person who obtained the consent—or worse.
Subject compromised by language, comprehension, or sedation.	Subjects who sign for themselves must be lucid and demonstrate that they understand the consent form content and process or the consent is invalid.
No addenda placed on consent or in medical record about special consent procedures used to accommodate to language or comprehension problems.	Special consent procedures must be documented in an explanatory note. An inspector or auditor should not have to guess about why signatures or names look unusual.
Signed by spouse on subject signature line (no explanation).	The spouse is not the subject. In cases where the spouse has the authority to sign, spouse must sign as authorized representative.
No medical power-of-attorney for spouse or other relative who signs for compromised subject.	In the absence of an emergency, consent should be given by the individual or by a person with legal authority to do so.
Several consents for different studies presented to subject at the same time, usually right before surgery; subject signs them all; only one becomes operable.	Reading and signing multiple consents "at the 11th hour" is unfair to the subject and probably constitutes invalid consents.
Subject's signature is different from signature on other hospital consents.	Sometimes, but not always, this can be explained by a subject's changing clinical status. The best support is good source notes documenting the subject's clinical conduct throughout the study.
Use of an outdated consent form.	Consent forms change because of IRB requests, protocol modifications, etc. Subjects must sign the most current version when they enroll.
Version of the consent document does not have items, or have items changed, that were requested by IRB.	The above comments apply to this problem also.
If principal investigators and sub investigators use different hospitals, subject signed the wrong hospital's consent.	When using local hospital IRBs, subjects must sign the consent approved by the particular hospital where the study procedure will take place.

ciencies, those that occurred in 50% or more of the consents, were the following missing items:

- Worldwide regulatory status of the investigational drug
- Person to contact about the trial or in case of emergency
- Common side effects of the investigational drug and their frequency of occurrence
- Trial treatments and probability for random assignment to each treatment.

Lin and the team concluded, however, that the consent forms they reviewed did, in general, comply with international guidelines.

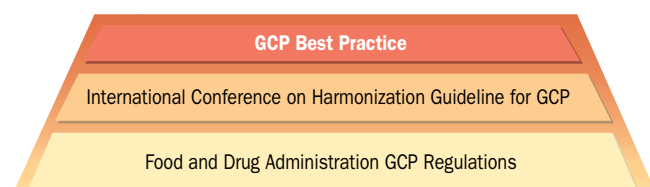
Previous research also stresses the subtle nature of the consent transaction. Mackintosh and Molloy suggested a simple improvement to the introduction of the consent form that establishes rapport with the reader.⁸ Sharp suggested improving the process of obtaining consent by including better, more skillful oral communication.⁹ Getz, in a recent online survey of subjects who completed a clinical study, found that in one in seven cases subjects stated that no one on the study staff reviewed the consent form with them, and a high percentage said that they did not know what questions to ask.¹⁰

Here, our purpose is to identify continuing problems in the delivery of study consent and to discuss reasons that these

issues plague the pharmaceutical, biotech, and device industries.

We apply three standards to this discussion. The least burdensome, as seen in the figure, are the FDA regulations specified in the *Code of Federal Regulations* and in guidance manuals. The next highest hurdle is represented by the ICH Guideline for Good Clinical Practice (4.3.3 and 4.8.10). The highest standard is in current thinking on the subject by industry, academia, and regulatory agencies. This standard is gleaned from recently published papers and from discussions with thought leaders. We apply all these standards, for which there is considerable overlap, to the discussion that follows.

First, we identify problems with content and readability. These issues include informed consent design and layout; next,



Three levels of standards that apply to informed consent process, according to current industry and academic thinking.

problems with the process of consenting subjects; then possible reasons that these sets of problems occur. Finally, we examine ways in which sponsors can prevent these problems.

Content and readability shortcomings

Table 1 displays frequently encountered problems with the content and readability of informed consents. The problems listed are from consents we examined that had been approved by IRBs and reviewed by sponsors and clinical department staff members. Below we highlight a few of the more significant problems in the tables.

Primary care physician notification. Despite being widely circulated in 1997, the ICH recommendation that the investigator inform a subject's primary care physician about enrollment in a study is rarely implemented (ICH Guideline for GCP, 4.3.3). As yet, we have not seen that mentioned in a consent form. Subjects sometimes fail to mention critical clinical information about their medical histories that would preclude enrollment. Thus, a subject's primary care physician might, in certain instances, warn the principal investigator about these conditions, thereby preventing a dangerous situation and nonevaluability.

Injuries. The study drug or the study's procedures could injure a subject. A mechanism should be in place to pay for treatment of medical injury. Often this mechanism is not fully described and has contradictory information that is confounded by discussion of the subject's health insurance.

Reproductive issues. Despite strong statements about birth control and pregnancy in study protocols, consent forms do not have sufficient warnings regarding pregnancy, requirements for pregnancy tests and birth control, and obligations should conception occur while on study. Given liability issues surrounding this topic, one would think that sponsors would insist on strong language in consents.

Placebos. The 2000 Declaration of Helsinki questioned the ethics of conducting placebo-controlled studies when an approved treatment exists. Yet placebo-controlled trials remain prevalent. It is, therefore, critical that subjects understand their chances of receiving a placebo and what can happen if they go undiagnosed or untreated. It is also important to understand what the alternatives are to enrolling in the study, especially if there is an approved treatment not offered as an arm in the study.

Subject obligations. A consent form is a kind of contract. Both parties to the agreement have obligations. Subjects must recognize that they have an obligation to inform study staff about their clinical conditions even if an abnormality seemingly has little to do with the study.

Language. Text that is too dense or is poorly displayed is intimidating and hinders comprehension. Simplifying, assisting in the flow of ideas, and avoiding confusion is an instructional design task requiring writing and layout skill and experience.

Consent process problems

Table 2 displays problems found in the process of obtaining consent from potential study subjects. Some of the more frequently encountered deficiencies follow.

Entry notes. Sites sometimes use a copy of the case report

form (CRF) inclusion/exclusion criteria as a source document to support a subject's eligibility and enrollment in a study. Instead, entry notes should be made in the subject's medical record. The time consent was obtained should be included to indicate that no study-specific tests or procedures were performed before obtaining informed consent.

Inadequate clinical background. A serious deficiency we encounter is when consent is obtained by a person who lacks sufficient clinical background to adequately explain the study requirements and answer questions. Complicated studies require substantial physician involvement.

Special procedures. Numerous problems emerge with special consent procedures, such as when the next of kin or a legal guardian signs the consent form. If an individual has legal medical power-of-attorney, that fact should be noted on the consent form. When a next of kin signs for a subject, the individual's relationship to the subject should also be indicated on the form. We often find that a spouse has signed on the subject signature line; but, because spouses who sign are not subjects, they should sign as the spouse on a different line. When no emergency situation exists, then only the person with legal signatory authority should sign for a subject.

Inappropriate timing. Study candidates sometimes are given multiple consent forms to read and sign just before a procedure such as cardiac catheterization. Some investigators say they do this because they are not sure for which study the candidates may qualify until after the procedure. Therefore, signing multiple consents is an "insurance policy" for the investigator. Study candidates cannot be expected to give truly informed consent under such high-pressure circumstances.

Why problems occur

Unrealistic expectations. As mentioned earlier, we examined content problems in consent forms that had been approved by IRBs. Study staff members often expect that an IRB-approved consent form is "perfect"—that it has no deficiencies. This is a false sense of assurance. IRBs frequently approve defective and suboptimal consent forms. It is the investigator's responsibility to obtain GCP-compliant consent.

Furthermore, we encounter IRBs and academic institutions that have outdated ideas and rules about what should and should not be written in consent forms. Some do not allow the listing of an IRB contact person. On the other hand, many central and national IRBs sometimes fail to sufficiently scrutinize consent forms for content, which can result in the omission of important information. Many IRB members, regardless of the type of IRB, do not devote sufficient time to reviewing and discussing critical consent content.

Fear of liability. Sponsors and institutions, particularly hospitals, are sometimes reluctant to take on additional liability for medical injury resulting from study drugs and procedures. The reluctance and efforts at "held harmless" clauses in contractual agreements lead to compensation for injury sections that are full of obfuscation and contradictory statements.

Poor editing. Consent forms are rarely proofread sufficiently. For example, we recently encountered an IRB-approved form in which the confidentiality section read, "Should the results of the study be published in the medical literature or presented at

scientific meetings, you will be identified either by name or any other manner." It appears that none of the 18 subjects enrolled at the site that used this consent form carefully read this section either.

Piecemeal process. The consent process can break down because it is sometimes a piecemeal process, spread out over several encounters between the patient and the care provider—and may involve more than one member of the study staff. Sometimes it's half subject recruiting—persuading a patient to sign up—and half going over the particulars of the study to obtain consent. In many cases, the physician performs the recruiting part, then a study nurse or coordinator discusses the fine points of the consent form with the subject.

Haste. The consent process is sometimes rushed, particularly when it occurs on the same day as surgery. We have encountered circumstances in which study subjects signed four different consents for four different studies just before cardiac surgery. Study mills sometimes conduct the consent process in waiting rooms. We once reviewed a medical record that documented that the subject was inebriated when he signed the consent.

Unqualified personnel. Sometimes an unqualified and/or untrained person, such as an investigator's secretary, conducts the consent process. For a very complex study, even delegating the consent process to a registered nurse is unacceptable. A medical assistant may, however, assist the investigator in obtaining consent for a simple two-week allergy study. That is, the qualifications of the person administering the consent process should match the clinical complexity of the study design, procedures, and risks.

Failure to understand relevant state legislation. Staff members who obtain consent from members of vulnerable populations, particularly minors and the aged, should be knowledgeable about state laws regulating assent and medical power-of-attorney. We have discovered too many instances in which the adult who signed for a minor was not that child's legal guardian and in which the person who signed the consent did not have medical power-of-attorney for the enrolled subject.

Implications of these findings

The consent process for clinical studies mirrors the consent process for hospital admissions and for elective surgery. The forms have too much fine print, "legalese," and obscure terminology. Subjects have numerous other concerns on their minds when they are asked to consent to enrollment in a clinical trial. Not all fear can be relieved—but improving the consent process can help alleviate some of a subject's understandable anxiety associated with impending medical tests and procedures.

Opportunities abound for improving the clinical trial consent processes and the content of the consent forms. Subjects must be given sufficient time to read and digest the information—and they need the time, opportunity, and encouragement to ask questions. As the process nears completion and the time for signatures approaches, site staff members can ask potential enrollees about their comprehension of study processes and risks and probe for unspoken reluctance and uncertainty about specific aspects of a study.

References

1. Donna Shalala, "Protecting Research Subjects—What Must Be Done," *New England Journal of Medicine* 343 (11) 808–810, 2000.
2. Ari Kiev, "A History of Informed Consent Doctrine," *Applied Clinical Trials*, May 1993, 56–69.
3. Denise Zanicchia, "Writing Readable Informed Consent Forms," *Applied Clinical Trials*, September 1992, 52–62.
4. Mark Hochhauser, "Writing, Reading, and Understanding Research Consent Forms," *Applied Clinical Trials*, May 1997, 66–73.
5. Mark Hochhauser, "The Informed Consent Form: Document Development and Evaluation." *Drug Information Journal*, 34 (4) 1309–1317, 2000.
6. National Cancer Institute, *NCI Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials* (NCI, Bethesda, MD, 1998).
7. Yeong-Liang Lin, et al, "Compliance of Clinical Trial Consent Forms With International Guidelines," *Drug Information Journal* 36 (1) 17–19, 2002.
8. Douglas R. Mackintosh and Vernetta J. Molloy, "Trade Secrets: Simple Improvement to the Content of Consent Forms," *Applied Clinical Trials*, January 2001, 56.
9. S. Michael Sharp, "Improving the Process of Obtaining Informed Consent," *Applied Clinical Trials*, January 2001, 32–38.
10. Kenneth A. Getz, "Informed Consent Process: A Survey of Subjects Assesses Strengths and Weaknesses," *Applied Clinical Trials*, November 2002, 30–36.

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