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Consent Forms: Let's Get the Basics Right

By Mark Hochhauser

As an institutional review board (IRB) member for almost 16 years, I've read a lot of consent forms and written extensively on the readability problems that are so common.[1-4] I also continue to be amazed at the frequent regulatory defects we see. Quality has not improved much over that time, partly because consent forms have grown much longer, even without the addition of HIPAA language and more frequent substudies (e.g., biomarkers, pharmacodynamics and pharmacogenetics). Longer consent forms provide more opportunities for defects. Too many consent forms are noncompliant with the regulations, inconsistent with FDA guidance, and contain basic grammatical and formatting errors. Who writes these consent forms? Who edits them? Who reviews them? We've received downright embarrassing consent forms from billion-dollar international drug and device companies that employ legions of regulatory specialists, attorneys and medical writers. If the sponsors can't get the consent form right, what else can't they get right?

Regulatory Compliance

The consent form for the notorious TeGenero TGN1412 study had 13 regulatory or ICH E6 Guideline – Good Clinical Practice defects.[5] Many other consent forms do not comply with regulatory requirements in the following ways:

Basic Elements

The basic elements of informed consent in 21 CFR 50.25(a) and 45 CFR 46.116(a) are fundamental and clearly spelled out in the regulations. Here are some examples:

> *…an explanation of the purposes of the research…*

It is reasonable to expect a consent form to clearly state the purpose of the research. Yet, the explanation in some consent forms is not understandable.

> *A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.*

Yet, some consent forms have omitted statements about the subject's right to refuse participation or discontinue their participation without loss of benefits.

> *The approximate number of subjects involved in the study.*

Yet, at least one consent form included no information on the number of subjects to be enrolled in the trial.

> *An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.*

FDA's "Guide to Informed Consent" (see below) clarifies:

> *The consent document should provide the name of a specific office or person and the telephone number to contact for answers to questions about: 1) the research subjects' rights; 2) a research-related injury; and 3) the research study itself.*

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Yet, some consent forms fail to mention the IRB, let alone provide subjects with a telephone number. Some tell subjects to contact the principal investigator, who may be causing the problem. Some advise subjects to contact the sponsor, who normally does not know who the subjects are because of privacy reasons.

Exculpatory Language

Some consent forms do not comply with the regulatory prohibition against exculpatory language in 21 CFR 50.20 and 45 CFR 46.116:

> *No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.*

Yet, we see such exculpatory language, such as:

- I expressly agree, as a condition of my participation in this study, that [sponsor] and IRB shall not in any manner be responsible for any injuries incurred as a result of my participation in the study and I waive, in advance, any claims against either and both of them.
- In the unlikely event that you are injured as a result of participating in this study, medical treatment will be provided or arranged by your doctor… Study sponsors…and your doctor will not provide financial assistance for medical or other injury-related costs and no medical compensation will be provided… [Doctor] can provide you with information about the general liability policies of this institution to determine if compensation may be available from that source.
- You hereby agree to hold harmless the…Institute…[researchers] and all other health care providers involved in any way in this study.
- You understand that this agreement is binding on you, your estate, your heirs and assigns, and extends to all liability of any nature whatsoever, including any claim for negligence or failure to warn. You hereby find yourself, your estate, your heirs and assigns, and any person or entity claiming to act on your behalf or on behalf of your estate, your heirs or assigns, not to make any claim against an person or entity whatsoever, for anything of value, arising out of the use, manufacture or distribution of this product.
- WAIVER OF LIABILITY; I, [name] and Dr. [investigator] grant a waiver or liability to the [institution] and its institutional Review Board. [sic]

According to the regulations, language that even appears to be exculpatory is not acceptable. The following language may appear to be exculpatory to anyone but an attorney:

- Giving you care [for a research injury] does not mean that [organization] or the researchers are at fault, or that there was any wrongdoing.
- Compensation for medical expenses shall not be deemed an admission of fault or liability by [sponsor] or its affiliates.
- Side effects, complications and/or injury, both expected and unexpected, are possible in any clinical study and can occur through no fault of your own, the study doctor, [institution], and the study Sponsor or its representatives.

When our IRB finds regulatory violations, we have no choice but to require that they be fixed before we can approve the study.

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FDA Guidance on Informed Consent

Too often, consent forms seem to be written with no understanding of FDA guidance. Almost every consent form we review requires changes to the substantive content. Revised consent forms are usually approved at the next monthly meeting. Sometimes, if the changes are minor, approval is conditional, based on the IRB chair approving the changes. Our IRB has completely rejected only a few studies for consent form changes that sponsors have been unwilling to make, but the delays are unfortunate.

In May 2009, the FDA updated its 1998 guidance on informed consent and changed the name of the document to "A Guide to Informed Consent – Information Sheet."

The following sections discuss a few extracts from this guidance, along with some examples of defective language from consent forms submitted to our IRB, from colleagues, and consent forms posted on the "Citizens for Responsible Care and Research" website (http://www.circare.org/WWA.htm).

Role of the IRB

> *IRBs have the final authority for ensuring the adequacy of the information in the informed consent document… Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, the IRB of record is the final authority on the content of the consent documents that is presented to the prospective study subjects.*

When our IRB has asked study sponsors to change language that we find unacceptable, the response has sometimes been, "No changes are acceptable." For example, one consent form included over two pages of risk information that the sponsor said could not be changed in any way. The "Serious side effects" section stated, "…a similar number of patients treated with placebo or [study drug] reported serious side effects," but did not describe the number or percentage of patients affected. The consent form stated, "Some patients treated with the study drug had abnormally high levels of liver enzymes in the blood. Most of these increases were temporary…," but did not clarify what it meant by "some patients," "abnormally high levels," "most increases," and "temporary."

It is understandable that sponsors do not want to deal with a multitude of consent form changes from different IRBs. However, problems like this put IRBs in the awkward position of accepting consent forms that, in the IRB's judgment, do not protect the subjects' rights or rejecting a study for minor reasons that the principal investigator, for example, is unlikely to appreciate.

Compensation for Research-Related Injuries

> *The consent document must explain whether there is compensation available in case of injury, but must not waive or appear to waive the rights of the subject or release or appear to release those conducting the study from liability for negligence. When no system has been set up to provide funds, the preferred wording is: "no funds have been set aside for", "[the cost] will be billed to you or your insurance," or similar wording that explains the provisions or the process. Wording such as: "will be your responsibility or that of your third-party payor" has been erroneously interpreted by some subjects to mean the insurance company is required to pay.*

Yet, we see inappropriate language in studies of experimental treatments, such as:

- In the event of a treatment-related injury, [sponsor] will reimburse you only for medical expenses for the treatment of bodily injuries that are not mentioned in this consent form as potential side effects and that are directly caused by the use of [study drug].

- Should you have a complication of [therapy] that requires medication or hospitalization, the study and/or its researchers will be unable to pay for those costs, and you and/or your insurance company will be responsible for the costs resulting from the complication.
- In the event you sustain an injury or illness as a result of participating in this research, please be aware that medical treatment for the injuries or illness will be available from [hospital]. The cost of the medical treatment may be the responsibility of you or your insurance company.
- In the event of physical injury or physical illness related to the study, no monetary compensation or subsidized medical treatment will be routinely provided to you by any person involved in this study, including the study doctors, the hospital, or the study sponsor… In the event of a product defect, standard terms and conditions of the product warranty will apply… [The consent form did not explain the standard terms and conditions of the product warranty. The warranty was not provided to the IRB for review. It may have been provided to subjects with the consent form, but product warranties are notoriously unreadable.]

Subject Understanding

Although not prohibited by the FDA regulations, use of the wording "I understand…" in informed consent documents may be inappropriate, as many prospective subjects will not "understand" the scientific and medical significance of all the statements… Subjects are not in a position to judge whether the information provided is complete… They should not be required to certify completeness of disclosure (e.g., "This study has been fully explained to me," or "I fully understand the study.")

Yet, we see inappropriate language, such as:

- I have read and understand all the information given to me in this informed consent document.
- I have read all parts of this informed consent form (or the information on the form was read to me) and have understood it.
- I have been fully informed by my doctor about the nature, significance and implications of the clinical study. I have read all parts of this Informed Consent Form or the information on the form was read to me and I have understood it.

A similar problem is asking the investigator to sign a statement that he or she cannot realistically certify, e.g.:

> According to my judgment, the subject has completely understood this information and agrees to participate in the study.

Better language for the subject would be: "I have read this whole consent form. All of my questions have been answered to my satisfaction."

FDA Approval

FDA also believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induce subjects. Subjects might think that because the IRB had approved the research, there is no need to evaluate the study for themselves to determine whether or not they should participate.

Yet, we see inappropriate language, such as:

- This research project/study and informed consent form were reviewed and approved by the [institution] Institutional Review Board for the protection of human subjects.
- The study protocol and this consent form have been carefully reviewed and approved by an independent review board or ethics committee at every site in the world that is now actively recruiting participants. These committees are set up to protect the rights and well-being of people participating in research projects like this one.
- This document has been approved by a committee that reviews investigational drug studies according to regulations that focus on the protection of the rights and welfare of participating subjects.

In my opinion, this language is less objectionable than other problems discussed in this article, but, in none of these examples, was it mitigated by language like, "Nevertheless, you should decide for yourself, in consultation with study personnel and other advisors, whether joining this study is a good decision for you."

Sloppiness

Many, if not most, consent forms do not comply with the ICH E6 Guideline 4.8.6:

> *The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.*

Readability problems due to complex sentences, passive case, technical terminology, and excessive length are common problems, but many consent forms have even more basic problems that can only be ascribed to sloppiness. Consent forms are prone to the same problems as any document when nobody is paying attention, such as:

- Sentences that begin with a lower-case word
- Bullet points without text
- Inconsistent font styles and sizes
- A mixture of fully justified and right justified paragraphs
- Inconsistent references to "patients," "volunteers," "people" and "subjects"
- Use of wrong words, such as "effect" instead of "affect," "independent review board" instead of "institutional review board," "complaint" instead of "compliant," "international normalized ration" instead of "international normalized ratio," and "DNA sample baking" instead of "DNA sample banking"
- Leaving the bottom half of a page blank in the middle of the document, so there is no way to know whether information has been inadvertently left out or there is just a formatting problem.

IRBs are sometimes chided for wasting time on typos, grammatical errors, and formatting problems in consent forms. I agree that IRB meetings should focus on human subjects protection and not turn into copy editing sessions, but why do IRBs need to see these problems at all? Any competent copy editor can catch such problems quickly and inexpensively.

Sloppy consent forms show a lack of respect for study subjects. They do not give study subjects confidence in the study. They communicate that the study is not important, thereby probably affecting enrollment, retention and protocol adherence. Why do sponsors

and investigators expect IRBs to swallow their pride and approve sloppy consent forms that reflect poorly on everyone involved?

Conclusion

IRBs have no choice but to reject consent forms that do not comply with the regulations. While compliance with FDA guidances is theoretically optional, it is asking a lot to expect IRBs to defend faulty consent forms at FDA inspections. Self-respect may require IRBs to request corrections of sloppy consent forms. Depending on investigator, sponsor and IRB timeliness, it can take months to correct faulty consent forms and obtain IRB approval. It is in everyone's best interests to ensure that IRBs receive consent forms that meet the highest standards of quality.

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