

**Medical College of Wisconsin IRB Guidance
on Negotiating Consent Document Language
for
Clinical Trial Sponsors**

1. Review and approval of the consent document is a responsibility that FDA assigns to the IRB with jurisdiction

The regulations governing FDA-regulated and federally-funded research (21 CFR 50, 56; 45 CFR 46) almost invariably required a robust informed consent process and documentation of informed consent prior to enrolling subjects. **The same regulations assign responsibility for reviewing and approving the investigator’s plan for pursuing and documenting informed consent to the institutional IRB or its proxy IRB.** Quoting from the FDA regulations, for example:

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. The IRB may require that information in addition to that specifically mentioned in 21 CFR 50.25 be given to subjects when in the IRB’s judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with 21 CFR 50.27 of this chapter, except as follows...

21 CFR 56.109

(a) In order to approve research covered by these regulations, the IRB shall determine that all of the following requirements are satisfied...

4. Informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with and to the extent required by 21 CFR 50.

5. Informed consent will be appropriately documented, in accordance with and to the extent required by 21 CFR 50.27...

21 CFR 56.111

See also the recently-published FDA draft guidance “Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors” (July 2014), where it states:

FDA requires that an IRB review and approve, require modifications in (to secure approval), or disapprove all research activities covered by the IRB regulations (21 CFR 56.109(a)). A critical part of this responsibility is for the IRB to ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in clinical investigations (21 CFR 56.109(b) and 56.111(a)(4)).

IRBs must review all materials used in the informed consent process. This includes recruitment materials and information provided in addition to the informed consent document (for example, a chart explaining what to expect at each study visit or a document explaining the costs to subjects). The IRB’s review is to ensure that information given to subjects as part of the consent process contains the elements identified in 21 CFR 50.25 and meets the requirements of 21 CFR 50.20 (see 21 CFR 56.109(a), 56.109(b), and 56.111(a)(4)).

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The IRB has the authority and responsibility to require that information given to subjects as part of informed consent be in accordance with 21 CFR 50.25. In its review of a clinical investigation, the IRB can disapprove a clinical investigation if informed consent will not be obtained in accordance with the informed consent regulations (21 CFR 56.111(a)(4)).

Investigators must use an IRB-approved written consent form when documenting informed consent, in accordance with 21 CFR 50.27, except as provided in 21 CFR 56.109(c). Thus, the IRB should review the adequacy and appropriateness of all wording in the consent materials, as well as the overall length and presentation of information. Consent forms that are long, complex, legalistic, and have a high reading level may overwhelm potential subjects and may inhibit reading of the full document and understanding of the relevant information.

The IRB should ensure that technical and scientific concepts and terms are explained, or common terms substituted, so that the anticipated subject population can understand all provided information (21 CFR 50.20). Pictures or diagrams may be used to improve understanding of medical terms of how an investigational product functions. IRBs may wish to evaluate, through subject interviews, how well the consent materials communicate critical information.

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All information given to subjects as part of the consent process is to be reviewed and approved by the IRB (21 CFR 56.109(a) and (b)).

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When new information or changes in the clinical investigation require revisions of the consent form (and any accompanying changes to the protocol), such revisions must be reviewed and approved by the IRB before the revisions are initiated, except when necessary to eliminate apparent immediate hazards to subjects (21 CFR 56.108(a)).

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FDA recommends that the clinical investigator provide the sponsor with a copy of the consent form approved by the IRB.

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2. Sponsor's role in Ensuring Compliance with 21 CFR 56

Quoting directly from FDA final guidance "Sponsor-Investigator-IRB Interrelationship Information Sheet: Guidance for Institutions Review Boards and Clinical Investigators" (June 2014)

FDA regulations (21 CFR 312.23(a)(1)(iv)) require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and IRB regulations (21 CFR 50 and 56). This requirement has been misinterpreted to mean that it is a sponsor's obligation to determine IRB compliance with the regulations. This is not the case. Sponsors should rely on the clinical investigator, who assures the sponsor on form FDA-1572 for drugs and biologics or the investigator agreement for devices that the study will be reviewed by an IRB. Because clinical investigators work directly with IRBs, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations.

An IRB must notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity (21 CFR 56.109(e)). This correspondence should be made available to the sponsor by the clinical investigator. In the Agency's view, this required documentation provides the sponsor with reasonable assurance that an IRB complies with 21 CFR 56 and that it will be responsible for initial and continuing review of the study. Also, the sponsor and, in fact, anyone who is interested, may obtain an Establishment Inspection Report from an FDA inspection of an IRB. These reports summarize the conditions observed during the IRB inspection. FDA, however, does not certify IRBs.

And also...

The sponsor may choose not to conduct, to terminate, or to discontinue studies that do not conform with the sponsor's wishes. For example, the sponsor, clinical investigator, and IRB may reach an impasse about study procedures or specific wording in an informed consent document. The FDA will not mediate such disagreements. The Agency's policy of decentralized ethical review of clinical investigations allows such decisions to be made by local IRBs, and any disagreements between a sponsor, IRB, and clinical investigator should be resolved through appropriate communication among those parties.

3. IRB consent document templates

In accord with the recommendations of FDA guidance ("Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors," July 2014), the MCW IRB has developed standard language in a standard format for all consent forms. On its website, the MCW IRB has published a family of consent document templates, each designed for a different type of study (e.g., clinical trial, non-clinical community interventions, observational studies, collection of data or biospecimens for future unspecified use), and a family of as-applicable scripted paragraphs (e.g., genetic studies, need to monitor any subject births). The MCW IRB requires its investigators to prepare consent documents within the parameters of these templates and scripted paragraphs.

Each of the consent document templates is published as a Microsoft WORD. The WORD version is provided to make it easy to edit drafts and so investigators may easily exchange drafts with sponsors.

4. Common sponsor concerns about the consent document

(a) Injury / liability language

The MCW IRB opposes the idea that contract liability details need to be repeated in the consent form. To quote FDA guidance again, “Consent forms that are long, complex, legalistic, and have a high reading level may overwhelm potential subjects and may inhibit reading of the full document and understanding of the relevant information.”

When an industry sponsor contracts with MCW for evaluation of an investigational article, the consent document language on compensation for injuries must read:

Emergency medical treatment for injuries directly related to your participation in this research study will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this study, contact the study doctors right away. Contact information: <PI>, <telephone number>

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

The MCW IRB believes that this paragraph contains basic and understandable criteria for defining a research-related injury, and lets the subject know that MCW will decide (with reference to the clinical trial contract) which party is responsible for compensation. There is no need to parse MCW versus Sponsor liability conditions in the study consent document.

If the Sponsor is offering to pay for research-related injuries, the template language can be changed to read ‘Sponsor’, where it currently reads ‘MCW’. The injury language is written broadly enough to avoid conflicting with the vast majority of Clinical Trial Agreements. As such, additional edits are not allowed.

(b) HIPAA language

HIPAA research requirements are satisfied by the immutable language in the consent document template -- the sections describing the study (A through D) fulfill some of the HIPAA requirements and the more HIPAA- specific sections E covers the rest. The MCW Compliance and General Counsel’s Offices have confidence that our document language and the specific details that the investigator is called upon to insert in the free text fields – summed across the entire document – include all the requirements of 45 CFR 164.501, 164.508, 164.512(i), 164.514€, 164.528, and 164.532.

(c) Consistency with previous versions of consent document language

The MCW IRB does not agree to match the language previous versions of consent documents used for a Sponsor’s studies at MCW because regulatory requirements/guidances are ever-changing and because the IRB perpetually tries to optimize the clarity and simplicity of the consent document.

5. Recourse for concerns about the consent document

- (a) **Access and study the PDF version.** It is possible that by identifying the free text areas of the consent document template, the sponsor will find that information deemed important can be entered under one of the relevant topical headings. The MCW IRB does not allow, however, interpolation of non-relevant information in a free-text section to in order to circumvent IRB guidelines.
- (b) **Discuss the Sponsor's concern with the MCW site principal investigator or study coordinator.** Most MCW investigators and study coordinators are familiar with the MCW IRB's approach to consent documents and institutional preferences. The study team members may be able to help the Sponsor identify a good solution. The study team members can discuss the concern directly with a member of the IRB office staff.
- (c) **Ask the MCW principal investigator to submit a "Petition to Change Informed Consent Form Required Language"** that MCW investigators can access on the same IRB webpage where they access research Consent Form Templates. A separate petition must be completed for each paragraph of mandatory language that the investigator proposes to alter, with justifications. The IRB rarely approves any changes to the immutable language.

If a Sponsor believes the IRB's decision to leave immutable language in a consent document template unchanged will result in either a clear inconsistency with the Sponsor/MCW contract or some form of regulatory non-compliance, the Sponsor may contact the IRB Manager to discuss this concern. The MCW IRB may or may not agree with the Sponsor's interpretation.

If after discussion with the IRB Manager, a Sponsor still believes the IRB's decision to leave immutable language in a consent document template unchanged will result in either a clear inconsistency with the Sponsor/MCW contract or some form of regulatory non-compliance, the Sponsor may contact the MCW IRB Director to discuss this concern. Again, the MCW IRB may or may not agree with the Sponsor's interpretation. The MCW General Counsel's Office and Corporate Compliance Office have confidence that the MCW IRB Director can make final decisions about consent document language, and so those offices do not feel the need to participate in these discussions. The decision of the MCW IRB Director in the matter of consent form language requirements is final and there is no further appeal.