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Recommendations for Study Sponsors on Anticipated Required Changes for Informed Consent Documents

Regulatory Background:

Over the last few years, the Office of Human Research Protection (OHRP), which oversees federally-funded research, has been working on revisions to the regulations for research oversight, including changes to informed consent and the process of Institutional Review Board (IRB) review.[1] These regulations are generally known as the "Common Rule", because multiple federal agencies have agreed to follow these regulations. Although the effective date of the regulatory changes has been delayed a few times, they will go into effect in January 2019.[2]

The OHRP does not have oversight of privately-funded (including biopharma funded) research. The revised OHRP regulations will not apply to research which is not under OHRP oversight. The Food and Drug Administration (FDA) has regulations that are largely similar to the regulations of the OHRP. The 21st Century Cures Act, passed in 2017, required that OHRP and FDA harmonize their regulations so that all human subject research is effectively being conducted under the same rules.[3] So while the revised Common Rule changes to informed consent will not apply to FDA-regulated research in January 2019, FDA has already made clear their intent to update their own regulations to become consistent with these changes.[4] In addition, many institutional IRBs may decide that they will apply the revised Common Rule regulations to all research they review, regardless of funding source, so that they don't have to keep track of more than one set of regulations, and which regulations might apply to different studies. Therefore, biopharma research sponsors who conduct FDA-regulated research may find themselves needing to make these changes well before the FDA regulations are formally changed.

This document is intended to summarize the regulatory changes that apply to informed consent documents, and to provide extra-regulatory and informal guidance where helpful, to help sponsors update informed consent document templates to be compliant with the new regulations. Please note that this document describes the regulatory interpretation and recommendations for meeting approval requirements for the WIRB-Copernicus Group IRBs*; other IRBs could have local institutional policies or approval requirements that differ from these.

* Western IRB, Copernicus Group IRB, New England IRB, Aspire IRB, Midlands IRB and Hummingbird IRB.

Changes to Informed Consent Documents

The changes that will be required to informed consent documents fall into two main areas:[5]

1. The inclusion of specific informational statements related to identifiable private information, commercial use of samples, return of results, and whole genome sequencing, when relevant to the research project
2. The inclusion of a "key information" section into the informed consent document

Informational Statements

The specific statements that must be included in the consent form, when they are relevant to the research project, are:

- "One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
  - (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
  - (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies."[6]
- "A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;"[7]
- "A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;"[8] and
- "For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)."[9]

Key Information

The regulatory changes include a new requirement for the organization and presentation of information in the informed consent document, as described in the new regulations.

> "Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension."[10]

The goal of this new requirement is to address concerns about the length and density of the written information provided to potential research participants, and to facilitate the presentation of information so that the most important facts related to the research study are not buried within the document and easily missed. The key information section is intended to include information "most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research". Providing this information in a concise, focused way is intended to improve the communication and understanding of information so that participants are better informed and prepared for study participation. Improved communication may result in higher rates of enrollment and retention in clinical studies, facilitating the efficient conduct of important clinical research.

There are five elements of information that are recommended in the preamble as likely to satisfy the key information requirement.[11]

1. The fact that consent is being sought for research and that participation is voluntary
2. The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research
3. The reasonably foreseeable risks or discomforts to the prospective subject
4. The benefits to the prospective subject or to others that may reasonably be expected from the research
5. Appropriate alternative procedures or courses of treatments, if any, that might be advantageous to the prospective subject.

While the term "reasonably forseeable" is not specifically defined, the term as used here is being understood to mean those risks that would perhaps have the most impact on the participant, their overall health and ability to function, as well as those that may be rare but could be significant. Risks that are included here may not necessarily be the most common risks; for example, in a study with multiple blood draws, bruising at the puncture site may be common, but a bruise is unlikely to have much impact on a participant's health or on their decision about whether to participate in the study.

In addition to the five recommended elements, the key information section should also include any additional significant information that is considered most likely to be informative to a potential research participant. This guideline, however, is highly subjective; what might be critically important information for one potential participant may be insignificant for another. Examples of what participants might consider to be most important might include things like

- The study requires a 30-day in-clinic confinement period
- The study requires abstaining from alcohol for six months
- During a study that will be several years in duration, women of childbearing potential may not become pregnant
- Participants who receive the investigational treatment may have limited options for future therapy for their illness

There is also no specific guidance on the length of the key information section. However, as an informal guideline, we recommend that the key information section should be no longer than 10% of the length of the overall document or three (3) pages, which ever length is shorter; that is, if the complete informed consent document is 20 pages, the key information section should be no more than about 2 pages. If the clinical study is a simple one and the informed consent document is brief—not more than 4-5 pages—we suggest that the key information section is not necessary, as the document would already be written in a way that is concise and focused.

These revisions to the informed consent document will require thoughtful and careful consideration by informed consent authors for each new study. The informed consent development process should include the participation of therapeutic areas specialists, clinicians and, when possible, patient representatives, who can represent the perspectives of potential participants.

Conclusion

As study sponsors, researchers and IRBs adjust to the new requirements, it is likely that there will be some adjustment and negotiation about informed consent content, and what factors about the study should be considered key information. While OHRP has stated that they recognize that more detailed guidance would be helpful to ensure compliance with this requirement, no additional guidance has been released yet. We will continue to provide information and guidance as it becomes available, and to assist in the interpretation of regulatory direction whenever possible.

Template documents to assist in the writing of a stand-alone informed consent summary, or a full informed consent that includes a summary section, can be found can be found in the Forms section of the websites for each of the WCG IRBs.

WIRB Forms
Copernicus Group IRB Forms
New England IRB Forms
Aspire IRB Forms
Midlands IRB Forms
Hummingbird IRB Forms

1 45 CRF 46 as published in the Federal Register , Vol. 82, No. 12, January 19, 2017. Rules and Regulations. Pages 7149-7274.

2 Revised Common Rule, Health and Human Services. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html. Accessed 25 October 2018

3 H.R.34- 21st Century Cures Act; Section 3023. https://www.congress.gov/bill/114th-congress/house-bill/34. Accessed 2 November 2018.

4 FDA Guidance "Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations." https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM623211.pdf. Accessed 1 November 2018

5 Revised Common Rule, 45CFR46.116(a)(5), (b)(9), (c)(7)–(9) and 45CFR46.117(b) Changes in the Elements of Consent, Including Documentation

6 Revised Common Rule, 45CRF46.116(b)(9)

7 Revised Common Rule, 45CRF46.116(c)(7)

8 Revised Common Rule, 45CRF46.116(c)(8)

9 Revised Common Rule, 45CRF46.116(c)(9)

10 Revised Common Rule, 45CFR46.116(a)(5)(i)

11 Federal Register , Vol. 82, No. 12, January 19, 2017. Rules and Regulations. Page 7214.