Key Information and Facilitating Understanding in Informed Consent

Guidance for Sponsors, Investigators, and Institutional Review Boards

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)

March 2024
Procedural

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) and the Office for Human Research Protections (OHRP) on this topic. It does not establish any rights for any person and is not binding on FDA, OHRP, or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA or OHRP staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations on provisions of the Department of Health and Human Services (HHS) regulations on the protection of human subjects as well as certain proposed revisions to FDA's current regulations for the protection of human subjects.[2] Specifically, this guidance addresses the presentation of key information and includes recommendations for the content, organization, and presentation of informed consent[3] information in FDA-regulated clinical investigations of drugs, devices, and biologics (collectively *medical products*) and in

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Office of Clinical Policy at the Food and Drug Administration, and the HHS Office for Human Research Protections.

[2] This guidance uses the term *human subject* or *subject* to describe individuals who participate in clinical investigations as defined by FDA's human subject protection regulations in 21 CFR 50.3(g) and 56.102(e), or who participate in human subjects research as defined by HHS's human subjects protection regulations in 45 CFR 46.102. We acknowledge that some interested parties may prefer other terms, such as *trial participant* and *research volunteer*, but we believe it is important to use the regulatory term in this guidance.

[3] The term *consent* is subsequently used in this guidance in place of *informed consent* for brevity and plain language, unless quoting regulatory language.

HHS-supported or -conducted nonexempt human subjects research.[4,5] The recommendations in this guidance should inform the communication of consent information to subjects, including prospective subjects or their legally authorized representatives, and may be conveyed by written, oral, or electronic means.

This guidance is intended to assist institutional review boards (IRBs), investigators, and sponsors engaged in or responsible for oversight of human subject research subject to FDA and/or HHS regulations with the development of consent information that would comply with 45 CFR 46.116(a)(5) and FDA's proposed revisions to 21 CFR 50.20(e), if finalized as proposed.[6] FDA-regulated clinical investigations conducted or supported by HHS are subject to both HHS and FDA regulations, per 45 CFR 46.101, 21 CFR 50.1, and 21 CFR 56.101.

In general, FDA's and OHRP's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA's regulations in 21 CFR parts 50 and 56 for the protection of human subjects are intended to protect the rights, safety, and welfare of human subjects participating in FDA-regulated clinical investigations and include requirements for informed consent and IRB review.

On January 19, 2017, HHS announced revisions to 45 CFR part 46, subpart A (the Common Rule), which are known as the revised Common Rule.[7] The revised Common Rule is intended to

[4] This guidance applies to FDA-regulated clinical investigations of drugs, biologics, or devices that are subject to 21 CFR parts 50 and 56, including investigations under 21 CFR parts 312 and 812. This guidance also applies to HHS-supported or -conducted nonexempt human subjects research that is subject to 45 CFR part 46. As used in this guidance, an *investigational medical product* is an investigational drug or biological product as defined in 21 CFR part 312 or an investigational device as defined in 21 CFR part 812.

[5] In this guidance, the terms *investigation, trial, study*, and *research* are used interchangeably and refer to clinical investigations regulated by FDA under 21 CFR parts 50 and 56 and to human subjects research subject to regulation by HHS under 45 CFR part 46, as applicable, unless otherwise noted.

[6] See FDA's notice of proposed rulemaking "Protection of Human Subjects and Institutional Review Boards" (87 FR 58733, September 28, 2022), available at https://www.federalregister.gov/documents/2022/09/28/2022-21088/protection-of-human-subjects-and-institutional-review-boards. As stated in the preamble, FDA intends to exercise enforcement discretion with respect to the proposed revisions to 21 CFR 50.20(d) through (e), 50.25(a)(9) and (b)(7) through (9), and 50.27(b)(2) for FDA-regulated studies that are ongoing when the proposed new requirements would become effective. In the event the proposed rule is not finalized as proposed, FDA intends to address any differences in future guidance.

[7] In this guidance, the phrase *revised Common Rule* refers to the final rule (82 FR 7149, January 19, 2017) codified in 45 CFR part 46, subpart A. It is also referred to as the 2018 Requirements. The term *harmonize* as used in

better protect human subjects involved in research, while facilitating research and reducing burden, delay, and ambiguity for the regulated community.[8] Prior to the most recent revisions to the Common Rule, FDA's regulations were largely consistent with the requirements in the Common Rule, with a few exceptions generally arising from differences in FDA's mission or statutory authority.

Section 3023 of the Cures Act[9] directs the Secretary of HHS to harmonize differences between HHS's and FDA's human subject protection regulations to the extent practicable and consistent with other statutory provisions. FDA has issued a notice of proposed rulemaking (the proposed rule) proposing to amend 21 CFR parts 50 and 56[10] in accordance with the harmonization requirement in the Cures Act.

III. KEY INFORMATION SECTION

The revised Common Rule requires consent information to "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" (45 CFR 46.116(a)(5)(i)). FDA's proposed regulations would add identical language to 21 CFR 50.20(e)(1).

The presentation of key information at the beginning of the consent process can help facilitate discussions between a prospective subject and an investigator about whether the prospective subject should participate in the trial. This information also may be useful to enrolled subjects as a resource and to facilitate any further discussions with investigators. We recommend that the key information section of a consent document[11] be relatively short (e.g., generally no more than a few pages). A sample key information section of a consent form for a hypothetical clinical trial is included in the appendix of this guidance. The format of the sample is based, in part, on research regarding how the presentation of information may affect consumers' understanding of

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FDA's proposed rule and in this guidance means "harmonize to the extent practicable and consistent with other statutory provisions," consistent with section 3023 of the 21st Century Cures Act (Cures Act) (Public Law 114-255). Some HHS-supported or -conducted research is not subject to the revised Common Rule per 45 CFR 46.101(l)(3) and is not required to address the provisions of the revised Common Rule addressed in this guidance.

[8] 82 FR 7149 (January 19, 2017).

[9] Public Law 114-255.

[10] See footnote 6. FDA previously has indicated in guidance that the provisions in the revised Common Rule related to the content, organization, and presentation of information included in the consent form and process are not inconsistent with FDA's current policies and guidances. See the guidance for sponsors, investigators, and institutional review boards *Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations* (October 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] In this guidance, the terms *informed consent form* and *informed consent document* are used interchangeably.

information found in labeling for prescription drugs.[12] Our recommendations in this guidance are not requirements, but are intended to provide considerations for how to present key information to prospective subjects.

For studies using a short form written consent in conjunction with an oral presentation of informed consent, the revised Common Rule at 45 CFR 46.117(b)(2) requires, and FDA's regulation at 21 CFR 50.27(b)(2) (if the rule is finalized as proposed) would require, that the key information be presented to a prospective subject or their legally authorized representative at the beginning of the informed consent process, before other information. Additionally, consent documents developed for FDA-regulated clinical investigations allowed to proceed under 21 CFR 50.24 ("Exception From Informed Consent Requirements for Emergency Research") would also be required to begin with a key information section.[13] Similarly, consent documents developed for expanded access use of an investigational drug would be required to begin with a key information section (21 CFR 312.305(c)(4)).

A. Flexible Approaches to Providing Key Information

There are multiple strategies for providing key information to prospective research subjects that would be consistent with the provisions of the revised Common Rule and FDA's proposed rule. Interested parties may consider developing an approach that encompasses principles from a variety of sources for the key information section, depending on the distinctive attributes and design of the study, the prospective subject population, the condition being examined, and other relevant factors. We encourage interested parties to develop innovative ways and utilize available technologies to provide key information that will help prospective subjects better understand the reasons why one might or might not want to participate in the research. Interested parties could consider developing alternate ways to present key information that would facilitate understanding by prospective subjects by, for example, consulting in advance with patient advocacy groups or prospective subjects about their views on key information. The key information section could also be presented using alternative media, such as illustrations, video, and electronic tablets, to meet the goals of improving clarity and increasing prospective subjects' understanding of consent information.

[12] Boudewyns, V, AC O'Donoghue, B Kelly, SL West, O Oguntimein, CM Bann, and LA McCormack, 2015, Influence of Patient Medication Information Format on Comprehension and Application of Medication Information: A Randomized, Controlled Experiment, Patient Educ Couns, 98(12):1592–1599, doi: 10.1016/j.pec.2015.07.003.

[13] Proposed 21 CFR 50.24(a)(6) (87 FR 58733 at 58749, September 28, 2022) would require an IRB to approve a consent document that meets the requirements of part 50 (including the key information provision) as a condition of authorizing an exception from informed consent requirements. See also the guidance for institutional review boards, clinical investigators, and sponsors *Exception From Informed Consent Requirements for Emergency Research* (April 2013). For research that is not FDA-regulated and is carried out under OHRP's Emergency Research Consent Waiver provisions (61 FR 51531-51533, October 2, 1996) for research where obtaining informed consent from subjects or their legally authorized representatives is not feasible, there is no key information requirement. Where consent is feasible, the consent process and documents must satisfy the key information requirement.

B. Identifying Key Information About Basic and Additional Elements of Informed Consent

We recommend that the key information section of the consent form begin with an introductory statement to frame the key information included in the consent form and to guide prospective subjects when reading the entire document. We do not recommend that the key information section of the consent form necessarily include each element of informed consent contained in 45 CFR 46.116(b) and (c) or in 21 CFR 50.25(a) and (b), including the proposed revisions to that section.[14]

One approach to developing the content of the key information section is for prospective subjects and other interested parties to advise on which basic and additional elements of informed consent may be considered "key" from the perspective of prospective subjects for a particular study. We recommend that the most important elements for a particular study be included at the beginning of the key information section.

Which basic and additional consent elements should be included in the key information section may vary based on factors such as the study attributes and its design; the condition(s), behavior(s), or outcome(s) being examined; and the prospective subject population. Basic and additional elements (or parts of such elements) of informed consent that are not addressed (or not fully addressed) in the key information section would need to be included elsewhere in the consent form as required (21 CFR 50.25(a) and (b) and 45 CFR 46.116(b) and (c)).

If appropriate, the elements of informed consent that are addressed in the key information section can also be repeated in other parts of the consent form. For instance, information about the most important reasonably foreseeable risks (e.g., most serious and/or most common adverse events) could be addressed in the key information section and could also be repeated with comprehensive risk information later in the consent form. Appropriate repetition of key information, particularly for longer and more-complex consent forms, can help clarify concepts and ensure that the entire consent form remains understandable to prospective subjects. We suggest using page numbers (or hyperlinks for electronic consent forms) to cross-reference information from the key information section to other sections of the consent form.[15] When the key information section encompasses all information for a required consent element (21 CFR 50.25(a) and (b) and 45 CFR 46.116(b) and (c)), further discussion regarding that element may not be needed in the remainder of the consent form.

Certain studies, such as those involving no more than minimal risk, may have relatively brief consent forms. In such cases, the key information section could constitute the majority of or

[14] For a full discussion of how to address the elements of informed consent during the informed consent process, see the FDA guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023).

[15] The terms *form* and *document* are not intended to discourage the use of electronic media and other innovative approaches to improving the consent form and process. For more information on electronic informed consent, see the FDA and OHRP joint guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016).

even the entire consent document. This approach may be acceptable as long as the entire consent document provides sufficient information to help prospective subjects make an informed decision about participation and the document includes all of the required elements of informed consent described in 21 CFR 50.25(a) and (b) and 45 CFR 46.116(b) and (c). If the entire consent form is the key information section, it does not need to be labeled "key information."

Our recommendations on how to address basic and additional elements of informed consent in the key information section are discussed in the topics that follow. These specific topics were selected because, in our view, these topics are likely to be considered key information for FDA-regulated clinical investigations and HHS-supported or -conducted nonexempt human subjects research. Some elements of informed consent, such as information regarding confidentiality of subject records under 21 CFR 50.25(a)(5) and 45 CFR 46.116(b)(5), are not addressed in this guidance, although they may be considered key information for some study designs.

The following topics, including the sample approach in the appendix, are intended to provide suggestions that we believe can help interested parties conducting research present key information in a concise and focused way that facilitates comprehension.[16]

1. Voluntary Participation and Right to Discontinue Participation[17]

A statement that consent for research is being sought and that participation is voluntary is a required element of informed consent, and we recommend that this element be included as key information. We recommend including a statement as part of key information that a prospective subject's decision not to participate in the study or to discontinue participation at any time will involve no penalty or loss of benefits to which the prospective subject is otherwise entitled. In some circumstances, interested parties may consider including a statement that assures prospective subjects that any decision not to participate in or to withdraw their consent from a study will not adversely affect their relationship(s) with or medical care received from health care providers.

2. Purpose of the Research, Expected Duration, and Procedures To Be Followed[18]

The key information section should convey information that is most likely to provide prospective subjects with a clear understanding of the purpose of the study and relevant details of the protocol (e.g., explaining in language understandable to prospective subjects that the study design is a randomized investigation with a placebo component). This approach to key information may include a simple description of why the research is being conducted and why the prospective subject is being asked to participate (e.g., due to the subject's diagnosis, the stage

[16] See, e.g., Freer, Y, N McIntosh, S Teunisse, KJS Anand, and EM Boyle, 2009, More Information, Less Understanding: A Randomized Study on Consent Issues in Neonatal Research, Pediatrics, 123(5):1301, doi: 10.1542/peds.2007-3860.

[17] 21 CFR 50.25(a)(8) and 45 CFR 46.116(b)(8).

[18] 21 CFR 50.25(a)(1) and 45 CFR 46.116(b)(1).

or status of their health condition, their lack of response to previous treatments, or other factors, such as inclusion of prospective subjects from different racial groups, ethnicities, gender identities, or socioeconomic status). The information should be explained in a way that promotes understanding of why a person might want or not want to participate.

Given the variability in the study design, the design details that are presented as key information will also vary. In many cases, key details of the design would include (1) the expected duration of the prospective subject's participation, (2) a high-level description of the major procedures involved, (3) a brief description of any investigational medical product and its marketing authorization status, and (4) identification of any experimental procedures, which for HHS-regulated research could include research procedures outside of a clinical research context (e.g., educational research).[19] It could be helpful to also include a discussion emphasizing the number of visits and time duration per visit so that prospective subjects understand the total time commitment involved with participating in the study.

When the key information section presents details about investigational medical products or other investigational interventions, interested parties should consider including information on whether the study design will include a placebo or whether a sham procedure (e.g., a procedure with a non-working device to blind the study design to avoid biasing results) will be used, how subjects will be assigned to a particular regimen (e.g., randomization), and what treatment or intervention options are available following the study (if any). Interested parties should also consider providing information on how an investigational medical product and/or participation in the study is similar to or different from the care the prospective subject would receive if not enrolled in the study.

3. Reasonably Foreseeable Risks and Discomforts[20]

The discussion of risks and discomforts is generally among one of the most important and complex required elements of informed consent, and we recommend that this topic be addressed in the key information section. We recommend providing information about the most common and serious risks and discomforts in the key information section to inform a prospective subject's decision about participation.[21] Key information about risks and discomforts of research participation should be included on the first page of the key information section, if possible. If the key information section does not include all risk-related information, the key information section should note that fact and include a page cross-reference (or hyperlink for electronic documents) that directs prospective subjects to the appropriate section of the consent form where complete information is located.

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[19] 21 CFR 50.25(a)(1) and 45 CFR 46.116(b)(1). For FDA-regulated clinical investigations, see the FDA guidance for IRBs, clinical investigators, and sponsors *Informed Consent*.

[20] 21 CFR 50.25(a)(2) and 45 CFR 46.116(b)(2).

[21] See, e.g., the Informed Consent Discussion Tool in Lentz, J, M Kennett, J Perlmutter, and A Forrest, 2016, Paving the Way to a More Effective Informed Consent Process: Recommendations from the Clinical Trials Transformation Initiative, Contemp Clin Trials, 49:65–69, p. 67, doi: 10.1016/j.cct.2016.06.005.

To help prospective subjects assess risks, interested parties should consider prioritizing key risks from any investigational medical products, research procedures, or other aspects of the study, at the beginning of the information about risks. It may be appropriate in the key information section to present only the most important risks or discomforts based on frequency or magnitude, rather than listing all reasonably foreseeable risks.[22] In clinical studies involving investigational medical products, the possibility that the product may present unknown risks to prospective subjects should generally be included as key information. Information about any potential risks should be explained in detail when possible, including, as applicable, the possibility that participation may not improve or could exacerbate a prospective subject's condition.

We recommend that interested parties clearly delineate between risks and discomforts associated with an investigational medical product or other investigational procedures (e.g., educational or behavioral health interventions) and the risks and discomforts associated with other research interventions or procedures (e.g., additional imaging studies that would not ordinarily be part of clinical care). Also, the degree to which the risks and potential benefits in the study are likely to differ from the risks and benefits of clinical care should be included as key information when appropriate.

In some cases, the key information section may include actions that will be taken to monitor and mitigate risks, such as planned safety monitoring, dose adjustments, or discontinuation of a subject's participation in the research.

4. Reasonably Expected Benefits[23]

Any reasonably expected benefits of participating in research, either to prospective subjects or others, are likely to be considered key information and could be a major determinant of whether a prospective subject decides to participate in a study. If there is no potential for direct benefit to the prospective subject, this point should be clearly stated. In general, for clinical research, it is important that prospective subjects understand that research is not the same as clinical care and that there may be considerable uncertainty about any potential benefits.[24] Details about any potential benefits of participation in a study should be presented in a manner that does not convey an inappropriate or overly optimistic representation of the facts. Potential benefits should be explained in terms of any direct impact to the prospective subject, in addition to the

[22] See Office for Human Research Protections, Attachment C – New "Key Information" Informed Consent Requirements: SACHRP Commentary on the New "Key Information" Informed Consent Requirements, October 17, 2018, available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html. The recommendations in this draft guidance concerning reasonably foreseeable risks in key information are consistent with SACHRP's recommended approaches.

[23] 45 CFR 46.116(b)(3) and proposed 21 CFR 50.25(a)(3), 87 FR 58733 at 58749 (September 28, 2022).

[24] The assumption of research subjects that decisions about their care are being made solely with their benefit in mind is termed *therapeutic misconception*. See Appelbaum, PS, LH Roth, and C Lidz, The Therapeutic Misconception: Informed Consent in Psychiatric Research, International Journal of Law and Psychiatry, 1982, 5:319–329.

anticipated societal benefit of the research. Any reasonably expected benefits of research participation should also be described in simple and straightforward terms. When appropriate, the description of the potential benefits should include an explanation of any potential impact on a prospective subject's health condition or illness. For example, if a clinical trial is being conducted to assess whether an investigational medical product may reduce tumor size, the key information section should indicate that it is unknown whether the investigational medical product will result in a change in tumor size and that if there is a change, it is not known if that change would affect the prospective subject's quality or length of life.

When evaluating potential benefits for inclusion in the key information section, we recommend that interested parties consider only those benefits that may result from the research (as distinguished from benefits of therapies or other interventions outside of a research setting (e.g., some behavioral interventions) that prospective subjects would receive even if not participating in research).

5. Appropriate Alternative Procedures[25]

In many circumstances, key information should include a clear and concise description of alternative procedures or courses of treatment, if any, that might be appropriate for the prospective subject. For clinical studies, consider first informing prospective subjects about care they would likely receive if not involved in the study and then providing them with information to help them understand how the care they would receive in the study differs. The emphasis should be on increasing awareness of alternatives because the choice between available alternatives is expected to vary based on individual values and preferences.

When conveying appropriate alternative procedures or courses of treatment, we recommend providing a description of any reasonably foreseeable risks or discomforts and potential benefits associated with these alternatives. However, a lengthy and detailed description of the risks and benefits of all alternatives may not be appropriate to include in the key information section because such information is likely to vary based on a prospective subject's health condition and past treatment experience as well as the type of study. All of this information need not appear in the key information section but should be included in the remainder of the consent document and as part of the discussion during the consent process.

6. Compensation and Medical Treatments for Research-Related Injuries[26]

For research involving more than minimal risk, we recommend addressing as key information details related to any medical treatments and compensation available to prospective subjects if injury occurs as a result of participation. Including this information as part of the key

[25] 21 CFR 50.25(a)(4) and 45 CFR 46.116(b)(4).

[26] 21 CFR 50.25(a)(6) and 45 CFR 46.116(b)(6).

information may be especially important when there are no plans to compensate prospective subjects for the costs related to the treatment of research-related injuries.[27]

7. Costs Related to Subject Participation[28]

We recommend that interested parties consider whether the key information section should also address costs the prospective subject may incur when participating in a study. If the sponsor or investigator intends to charge for the cost of tests, procedures, products, and/or interventions (including interventions outside of a clinical setting) used during the study, information about costs that may be incurred by a prospective subject or whether the prospective subject's health insurance could be charged (along with information on how to determine whether health insurance will cover costs) should be included in the key information section. The key information section could also inform prospective subjects about whether they will be reimbursed for study-related expenses (e.g., mileage, parking, airfare, lodging, childcare) because such information may influence a prospective subject's decision to participate. Similarly, incentives to encourage participation, as well as payments for a prospective subject's time, inconvenience, and/or discomfort, may be appropriate to include as key information.

C. Supplemental Information That Could Be Included Within Key Information

While not required, supplemental information beyond the basic and additional consent elements may be included in the key information section when it is likely to be important to the prospective subject's decision about research participation. For example, an investigator conducting a study that could involve risks to others not participating in research (e.g., radioactive interventions, potential shedding of a virus in gene therapy studies) may want to highlight in the key information section the potential risks to these third parties.

Identifying information beyond the basic and additional elements of informed consent that an investigator might want to include with the key information can be complex. The Secretary's Advisory Committee on Human Research Protections (SACHRP)[29] has provided recommendations on approaches to providing key information consistent with the provision included in the revised Common Rule.[30] For example, SACHRP addresses several approaches, including preparing the key information section from a prospective subject's perspective by

[27] For ways to address compensation, medical treatments, and information for research-related injuries, see the FDA guidance for IRBs, clinical investigators, and sponsors *Informed Consent*.

[28] 21 CFR 50.25(b)(3) and 45 CFR 46.116(c)(3).

[29] See footnote 22.

[30] Ibid. See also 45 CFR 46.116(a)(5)(i).

keeping certain questions about the research in mind. The following list of questions is consistent with, but not limited to, SACHRP's recommendations:[31]

(1) What aspects of research participation or this particular study are likely to be unfamiliar to a prospective subject, to diverge from their expectations, or to require special attention?

(2) What information about prospective subjects is being collected as part of the research?

(3) What are the plans to share and protect data that may be of concern to a prospective subject?

(4) What impact will participating in this research have on a prospective subject outside of the research? For example, will it reduce options for standard treatments, prevent prospective subjects from accessing future care or from participating in other studies, or impact personal activities such as driving or sun exposure?

(5) How will a prospective subject's experience in this study differ from treatment outside of the study?

(6) How is this research novel?

(7) What investigator's conflict of interest (if any) may be of interest to prospective subjects?

(8) How can prospective subjects access any investigational medical products or other interventions examined in the study following completion of the study?

The answers to these and similar questions can be used to help identify information that could be appropriate to include with the key information for a given study. We note that this list is not exhaustive and should not be used as a checklist.

D. Example of Key Information Section

The appendix to this guidance presents one example of an approach to key information that may be considered by interested parties when developing a key information section and may be considered by IRBs when reviewing consent forms. The language and formatting used are offered as suggestions only, and other language and formatting may be used where appropriate. Depending on the study, it may be appropriate for the key information section to include other informed consent elements from those selected for the example.

[31] See appendix I in the Office for Human Research Protections, Attachment C – New "Key Information" Informed Consent Requirements: SACHRP Commentary on the New "Key Information" Informed Consent Requirements, October 17, 2018, available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html.

IV. FACILITATING UNDERSTANDING

The revised Common Rule at 45 CFR 46.116(a)(5)(ii) requires that "informed consent as a whole must present information in sufficient detail relating to the research and be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate." This provision applies to the consent document as a whole, and the principles are also expected to be applicable to any presentation of consent information (e.g., written, oral, or electronic).[32] FDA's proposed revisions to its regulations at 21 CFR 50.20(e)(2) would also include this requirement.[33] Our recommendations on how consent forms can be organized and presented in a way to facilitate understanding are included in the following sections.

A. Using Bubbles for the Key Information Section

To help present key information in a simple, concise format, we recommend that interested parties consider organizing information within a defined border (e.g., rounded boxes creating a discrete unit of information), referred to here as *bubbles,* or another format that makes the content easy to read and understand. (See the appendix to this guidance for an example of the bubble format for the key information section.) Discrete bubbles addressing separate topics, such as the purpose of the research, potential risks, or alternative therapies, may facilitate a prospective subject's understanding of the information.[34]

Research has explored consumers' comprehension of alternative versions of prescription drug labeling information to assess whether certain formats improved comprehension.[35] The research found that consumers had better comprehension when information was provided in a simple format, with information organized or grouped together within a defined border (e.g., rounded boxes creating a discrete unit of information that can be thought of as a bubble).[36]

In addition to using the bubble format or a similar approach for the key information section, other helpful approaches to formatting and organization could be used, including formatting text into two columns, using bullet points to simplify long explanations, and including ample white

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[32] See the FDA and OHRP joint guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers*.

[33] Proposed 21 CFR 50.20(e)(2) (87 FR 58733 at 58749, September 28, 2022).

[34] See footnote 12.

[35] Ibid.

[36] Ibid. (See page 1597 in Boudewyns et al. (footnote 12)). Note that this article compared three formats, including a bubble format in which rounded boxes were aligned in two vertical columns and a format used for over-the-counter (OTC) medications that organized information into boxes that ran the width of the page. A third approach with paragraphs followed the MedGuide format and was used as a control.

space or empty space around discrete bubbles. Such formatting approaches may make documents easier to read.[37]

B. Organization and Presentation of the Entire Consent Form

The revised Common Rule at 45 CFR 46.116(a)(5)(ii) requires, and 21 CFR 50.20(e)(2) of FDA's proposed rule would also require, that consent information be presented in a way that facilitates the understanding of prospective subjects, and, like the key information provision, could also be addressed in multiple ways. We recommend following plain language principles for the entire consent form.[38] Plain language principles generally involve a combination of text-based and visual approaches (e.g., pictures and diagrams), including organizing information with the most important points first, breaking complex information into understandable groups, using simple language, and defining technical terms.[39] The use of bubbles beyond the key information section may not be feasible. However, we suggest that interested parties consider using other formatting suggestions discussed in section IV.A of this guidance (e.g., bulleted lists, two-column format, white space), as appropriate, for the entire consent form.

1. Providing Content in Sufficient Detail

The revised Common Rule at 45 CFR 46.116(a)(5)(ii) requires, and 21 CFR 50.20(e)(2) of FDA's proposed rule would also require, that the consent "present information in sufficient detail relating to the research." This provision applies to information that is required to be included in informed consent. Sufficient detail about research information may be contained within a key information section or elsewhere in the consent form, depending on where it is most appropriate.

2. Organization

The revised Common Rule at 45 CFR 46.116(a)(5)(ii) requires that informed consent as a whole "be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate." FDA's proposed rule, if finalized as proposed, would include identical language in 21 CFR 50.20(e)(2).

Thoughtful organization of consent documents can help prospective subjects better understand the information presented in the entire consent form. One suggestion would be to use a tiered approach, particularly for more-complex study designs.[40] The first tier would provide the key

[37] Ibid.

[38] See Hadden, KB, LY Prince, TD Moore, LP James, JR Holland, and CR Trudeau, 2017, Improving Readability of Informed Consents for Research at an Academic Medical Institution, J Clin Trans Sci, 361–365, doi: 10.1017/cts.2017.312. Also see footnote 21.

[39] See footnote 12.

[40] See footnote 21.

information. The second tier could be divided into different topics with the remaining consent elements (or with further details of consent elements partially addressed in the key information section). A third tier could address other information that is not required by the regulations or could provide details of required elements, such as a detailed description of the study design, a schedule of procedures at each visit, and language about how confidential information may be handled. If appropriate for the consent form, the third tier also could include glossaries and references. We recommend including a table of contents and page numbers (or hyperlinks for electronic documents) to cross-reference related topics.

3. Understandable Language

Information should be presented in plain language and at a level prospective subjects would likely comprehend; explanations should be included for scientific and medical terms.[41] An assessment of the needs and characteristics of the prospective subject population, including their age, any relevant medical diagnosis, level of English proficiency, education level, and cognitive abilities, can be helpful in developing consent information that facilitates understanding. Information should be provided in the primary language of a prospective subject with limited English proficiency.[42] Although not required, one possible way to evaluate whether the information is presented in a way that facilitates understanding is to have the information reviewed by individuals unfamiliar with the research. This may be particularly helpful for forms translated into additional languages. For example, this could include review by patient advocacy groups or a sample of individuals from the subject population.

[41] See Jefford, M, and R Moore, 2008, Improvement of Informed Consent and the Quality of the Consent Form, Lancet Oncol, 9(5):485–493; p. 489. Also see footnote 38 and footnote 21.

[42] FDA and OHRP strongly encourage stakeholders to ensure that informed consent documents are accessible to individuals with limited English proficiency. To the extent an organization receives Federal financial assistance from HHS, the organization must comply with Title VI of the Civil Rights Act of 1964 and its implementing regulations. This guidance provides information to assist IRBs, investigators, and sponsors in complying with OHRP's regulation and FDA's proposed regulation, if and when it is finalized, related to the key information section of informed consent. This document does not provide guidance on how to comply with any regulatory obligations stemming from a source outside of the statutes FDA and OHRP administer and their respective regulations.

APPENDIX: A HYPOTHETICAL CLINICAL TRIAL

Title: A trial to evaluate the use of product X to treat health condition Y

Key Information You Should Know Before Agreeing to Participate

The key information that follows can help you learn more about this clinical trial. It can also help you decide whether or not to take part in the trial. **Please read the entire consent form or have someone read it with you.** If there is anything that you do not understand, please talk to the trial doctor or team to have your questions answered before signing the consent form.

Voluntary Participation and Right to Discontinue Participation

We are asking you to consent to participate in this research study. Your participation is voluntary and should be based on what is important to you. It is your choice to participate in this trial. If you agree to participate, you may leave at any time without penalty or loss of benefits to which you are otherwise entitled.

Purpose of the Research

The purpose of the trial is to find out if product X, the product that is being studied, is safe and effective in treating adults like you who have health condition Y.

Key Reasonably Foreseeable Risks and Discomforts (see page #)

- If you take product X, you have a chance of side effects, such as fever or rash.
- Nausea or vomiting may be related to your health condition and is a rare but serious side effect of product X. If product X is suspected to cause these or other symptoms, product X may be stopped.
- We do not know if product X will help you. There is a chance that product X could worsen condition Y.
- More information on risks is available in the consent form.

Reasonably Expected Benefits (see page #)

- Prior research suggests product X may improve condition Y.
- Researchers are studying product X in this trial to learn more about whether product X will improve condition Y.
- If you are randomly assigned to take product X, product X may improve your health condition Y. If you are randomly assigned to take the inactive pill, you will not receive product X and will not benefit directly.
- By participating in this trial, you will help researchers learn how product X may help people with condition Y.

~ MORE ~

Expected Duration and Procedures to Be Followed (see pages #)

- To learn if product X makes a difference, it is important for the trial to include people who will get a placebo (inactive pill). With this information, researchers can compare the effects of product X or the placebo on your health condition.
- A computer will assign you randomly, like flipping a coin, to a group taking product X or to a group taking the inactive pill.
- You and your doctors cannot choose which group you will be assigned to.
- This trial will take 6 months and require weekly clinic visits (24 visits total), with each visit expected to take 1 hour. At each visit, you will have blood drawn and a procedure to test your blood oxygen content.

Appropriate Alternative Procedures (see page #)

- In this trial, if you are assigned to take the placebo, you cannot take product X.
- Before joining the trial, you should talk to your doctor about alternative approved treatment options for your condition, and whether or not this trial is a good choice for you.
- Before agreeing to join, you should review information in the rest of the consent form.

Compensation and Medical Treatments for Research-Related Injuries (see page #)

- If you experience an injury caused by your participation in this research, the medical treatment of your injury will be paid for.
- More information on medical treatments for research-related injuries is available in the consent form.

Costs Related to Subject Participation (see page #)

- You may incur costs by participating in this trial.
- The sponsor will reimburse you for any travel costs for mileage, parking, and other expenses.
- In addition, the sponsor will pay you for your time participating in the trial.

Additional Information (see page #)

- If trials show that product X is effective in treating your health condition, you may be able to continue to take product X in a related trial.