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governance, ethics, evidence, policy, practice

Public Comment:
Docket No. FDA-2022-D-2997_Draft Guidance - Key Information and Facilitating Understanding in Informed Consent - Guidance for Sponsors, Investigators, and Institutional Review Boards

30 April 2024

Dear FDA Colleagues:
We very much appreciate the opportunity to share our observations and suggestions on this important draft guidance.

For your reference, the GE2P2 Global Foundation is a U.S.-headquartered, global NGO founded in 2016 as a spin-off of the Division of Medical Ethics at the NYU School of Medicine. Our mission is to advance scientific rigor, ethical resilience and integrity in research and evidence generation. Our key focus areas include biomedical and genomic research, complemented by our work across health, human rights, humanitarian action, education and sustainable development.

As part of this mission, we monitor and engage calls for input, comment, and public consultation on draft laws, regulations, policies, guidance and other deliberative processes undertaken by nation states and their regulatory bodies, multilateral agencies and the UN system overall, INGOs and civil society organizations, and non-state actors. This public consultation activity is undertaken by the Foundation's community of practice – researchers, scientists, ethicists, multilateral agency leaders, government and ministry officials, INGO leaders, and field practitioners operating in 30+ countries.

The GE2P2 Global Foundation also functions as the secretariat for the Global Forum for Research Ethics and Integrity [GFREI] – a global group of individuals from over 33 countries who collaborate on analysis and action including response to public consultation opportunities primarily focused on global health and biomedical research.

On behalf of the GE2P2 Global Foundation, I am pleased to submit these comments as attached.

David R. Curry
President & CEO

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General Comment

Overall, we find this draft to be well conceived, comprehensive, and fit for purpose in addressing "…the presentation of key information and [in providing] recommendations for the content, organization, and presentation of informed consent information in FDA-regulated clinical investigations…"

We present our line-level observations and recommendations below, but focus here on a key matter the draft is silent on: assent and how key information sections in assent documents might best support study subjects in considering their participation in research.

Of course, assent is well anchored at 45.46.408 [https://www.ecfr.gov/on/2018-07-19/title-45/section-46.408] and 21.50.55 [https://www.ecfr.gov/current/title-21/section-50.55].

It is entirely unclear why this guidance should be silent on assent.

If there is a compelling rationale for not addressing assent here, we urge FDA to be clear about it in the introductory sections of the draft. If there is not a compelling rationale, we urge FDA to review the guidance overall and to develop language addressing it at all the points where it would be helpful to the intent of the guidance.

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Line-Level Observation[s]/Suggestions/Suggested Edits

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FDA Guidance Draft – Repeating Key Information Elements in ICF

> 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

Observation[s]/Suggestions

We note that *Lines 136-37* suggest that "if appropriate" elements of the key information section "can also be repeated" in other sections of the informed consent form. We assess that a participant should enjoy an expectation that language in the key information section is derived from the fuller discussion in the overall ICF. Further, it should be straightforward to find this fuller discussion language in the ICF, helpfully flagged by the inclusion of the key information text. Indeed, we assess that elements in the key information section should, at a minimum, include page references or other mechanisms to assist the participant in *finding* the fuller discussion.

Suggested Action[s]/Edit[s]

136. ~~If appropriate,~~ The elements of informed consent that are addressed in the key information section **should be** repeated in other parts of the consent form **where fuller discussion is presented. In addition,**

the key information section elements should reference the page number[s] where fuller discussion is presented in the ICF to assist the participant in navigating to that language.

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FDA Guidance Draft - Confidentiality of subject records

> 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.

Observation[s]/Suggestions

We note that *Lines 161-163* reference "…information regarding confidentiality of subject records under 21 CFR 50.25(a)(5) and 45 CFR 46.116(b)(5)…" but that this issue is "not addressed in this guidance, although they may be considered key information for some study designs." We assess that data privacy is a significant matter and a growing issue across may study designs. We are therefore concerned that this guidance would be silent on this area.

Suggested Action[s]/Edit[s]

We urge FDA to engage confidentiality of subject records in this guidance via a careful analysis and guidance language aligned with the solid treatment of issues evidenced across the draft.

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FDA Guidance Draft – Voluntary Participation/Withdrawal

> 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.

Observation[s]/Suggestions

We assess that *Lines 169-179* provide a robust discussion of voluntary participation and the right to discontinue participation in a given study. We observe that there is an important dimension associated with the right to withdraw that is not addressed: that the participant's decision should be considered private, that the reasons or rationales behind the decision do not have to be disclosed, and that the participant is not required to participate in interactions where investigators seek to identify reasons for withdrawal or explore potential actions to mitigate reasons for the decision, or to change the decision.

Suggested Action[s]/Edit[s]

We urge FDA to add language at *Line 179* which clarifies that a participant's decision to withdraw is private, that reasons or rationales behind the decision do not have to be disclosed, and that there is no requirement to participate in interactions where investigators may seek to identify reasons for withdrawal or explore potential actions to mitigate reasons for the decision or to change the decision.

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FDA Guidance Draft

> 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.

Observation[s]/Suggestions

We note that *Lines 200-202* usefully reference the inclusion of the "number of visits and time duration" in the key information section as potentially helpful for participants. While this information will vary widely across study designs, we note that that some types of studies [e.g. genomic medicine-related studies/gene therapy trials] involve long-term follow [LTFU] which may require visits ranging out to a decade or more. We suggest some reference to LTFU in this section.

Suggested Action[s]/Edit[s]

200. **…**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. **Where the study design will include LTFU [long-term follow up] to assess risks, progress against study end-points, or to collect ongoing patient data, such information should be included in the key information section.**

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FDA Guidance Draft – Risk Mitigation in "Key Information"

> 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.

Observation[s]/Suggestions

We note that *Lines 245-247* state that "…the key information section may include.." information about monitoring and/or mitigation actions involving study risks. We understand that clear articulation of risks is an integral dimension of consent and we urge that the key information section include specific reference to monitoring/mitigation action, even if it is to note that no specific monitoring and/or mitigation actions are planned in the study design. In short, it should not be an option to be silent on this, whether the study design includes or not does not include such action.

Suggested Action[s]/Edit[s]

245 ~~In some cases,~~ The key information section **should reference** 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. **If no such actions are part of the study plan, the key information section should state this [for example, as a closing bullet in the Appendix at *Line 501-504*].**

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FDA Guidance Draft – Study-related Injury

> 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 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]
>
> [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*.

Observation[s]/Suggestions

We note that *Lines 296-300* state that information about medical treatments and compensation for study related injury "…may be especially important when there are no plans to compensate prospective subjects for the costs related to the treatment of research-related injuries." We are concerned that this language suggests that studies could proceed responsibly *without* provision for medical treatments and compensation aligned to the given study design.

Suggested Action[s]/Edit[s]

We urge FDA to add clarifying language and/or examples of where the absence of such provisions could be considered as responsible study design and the associated risks.

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FDA Guidance Draft - Compensation

> 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.

Observation[s]/Suggestions

We note that *Lines 314-315* suggest that it "may be appropriate" to include information about " incentives to encourage participation, as well as payments for a prospective subject's time, inconvenience, and/or discomfort" in a key information summary. We assess that this area of study participant compensation is both important and evolving quickly: it *should* indeed be addressed in key information.

We are seeing more regular reference in guidance to substantive compensation [e.g. for controlled human infection studies [CHIS]] and the emergence of compensation which could involve intellectual property [IP] benefits and profit-sharing [see WHO guidance in development: *Invitation for Public Comment: WHO principles for human genome access, use and sharing* - 8 April 2024]. Equally, concerns about "inducement" to participate cut across this trend.

Suggested Action[s]/Edit[s]

314 Similarly, incentives to encourage participation, as well as payments for a prospective subject's time, inconvenience, and/or discomfort, **should be included as key information where part of a study design.**

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FDA Guidance Draft

> **A. Using Bubbles for the Key Information Section**
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> 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]

Observation[s]/Suggestions

We assess *Lines 378-392ff* to helpfully introduce the role and importance of information design in facilitating participant comprehension and retention of ICF content. Equally, we recognize that "design value" and informed consent is an area deserving more focus in research and in the literature.

The draft guidance leads section *IV/ Facilitating Understanding* with the discussion as above around "using bubbles" and further presents a treatment of a key information sections in *Appendix A* using this "bubbles approach."

While we strongly support engaging design here, we are concerned that this guidance as presented will likely generate a "bubbles paradigm", influencing ICFs for at least the near-to-medium term. We assess that any design approach which would likely have such an impact on practice should be grounded by solid evidence.

However, the guidance limits the evidence it cites for use of bubbles to a single study from 2015 that involved "patient medication information handouts for a fictitious drug" [not an ICF or consent content]. Further, we note that this study has been cited 28 times since 2015, which may or may not be a healthy citation performance in the patient medical information handout field.

> 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.

Suggested Action[s]/Edit[s]

We urge FDA to significantly alter this section to soften the apparent imprimatur of a "bubbles paradigm" unless more substantive evidence is identified and evaluated. Indeed, we assess that new research might be commissioned to explore and quantify the impacts of information design strategies, specifically with consent content as its focus. This might include a systematic review.

We are aware of recent work, such as Holtz et al below, which might assist developing a strategy around this recommendation.

> **Enhancing comprehension of online informed consent: the impact of interactive elements and presentation formats**
> *Research Article*
> Bree Holtz, Katharine Mitchell, Robyn Adams, Caitlin Grier, Jason Wright
> *Ethics & Behavior*, 29 March 2024
> Abstract
> Informed consent, a cornerstone of research ethics, ensures participant protection and informed participation, particularly in online settings. Despite its significance, engagement with online consent forms remains low, underscoring the need for improved presentation strategies. This study investigates the impact of interactive elements and diverse presentation formats on the comprehension and engagement of online informed consent documents among a broad demographic beyond the commonly studied student populations. Employing a between-subjects experimental design, we explored six versions of online consent forms varying in interactivity, readability, and visual formatting to identify optimal strategies for enhancing participant comprehension and engagement. Our findings reveal that interactive formats significantly improve comprehension and perceived readability, highlighting the pivotal role of design in facilitating informed consent. The study also examines the influence of individual differences, such as self-efficacy and trust in science, on the effectiveness of consent forms, providing insights into the nuanced dynamics between participant characteristics and consent form engagement. These results advocate for integrating interactive elements and thoughtful design in consent forms to foster a more informed and engaged participant base. Implications for research ethics, best practices in consent form development, and future research directions are also discussed, emphasizing the need for ongoing innovation in the consent process to adapt to the evolving landscape of online research. This study contributes to the body of knowledge on research ethics by offering evidence-based recommendations for enhancing the informed consent process, ultimately promoting participant-centered research practices.

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