Brigham and Women's Hospital
Founding Member, Mass General Brigham

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

September 5, 2023

US Food & Drug Administration
Submitted: https://www.regulations.gov/commenton/FDA-2023-D-1955-0002

Re: E6(R3) Guideline for Good Clinical Practice; International Council for Harmonisation; Draft Guideline for Industry (ID FDA-2023-D-1955-0002)

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the International Council for Harmonisation (ICH) and the US Food & Drug Administration's request for input and comments on the draft guideline for industry entitled "E6(R3) Guideline for Good Clinical Practice." We appreciate the thoughtful modifications proposed in the E6(R3) guideline that recognize the modernized considerations needed to guide the design and conduct of modern human subjects' research.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it is an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. While the MRCT Center often collaborates and interacts with the FDA, we have not discussed the comments provided herein with anyone at the FDA. The responsibility for this document's content rests with the MRCT Center's leadership, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

The MRCT Center applauds the overall structural redesign of the E6(R3) GCP guideline and enthusiastically supports the proposed changes. In this context, we have identified specific areas that we believe, with revision and improvement, will further protect the rights, safety and well-being of all trial participants. We respectfully submit the following comments for consideration:

[1] Brigham and Women's Hospital, Ropes and Gray LLP, Harvard Medical School, and Harvard University.

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The Ethical Review of Clinical Trials

III.1. Institutional Review Board/Independent Ethics Committee (IRB/EC): We appreciate the draft guideline recognizes that "IRB/IECs are responsible for the ethical review of the trial" (line 269) and states that "The purpose of an IRB/IEC is to safeguard the rights, safety, and well-being of all trial participants" (line 273). The draft guideline has historically and currently identified the regulatory and administrative responsibilities of the IRB/IEC; however, it does not provide equal emphasis on the risk/benefit analysis that IRBs must weigh throughout the life of the trial. Moreover, we are concerned that IRBs/IECs may be more focused on compliance with regulations, and less concerned (and therefore less knowledgeable) about ethical issues (e.g, minimization of risk, risk and benefit assessment, choice of comparator, inclusion/exclusion criteria to ensure appropriate inclusion and representation in clinical trials, decreasing burden of participation [reimbursement and compensation, travel, language concordance and translation, etc.], return of results to participants, access to therapies at the end of trial, causality of adverse events). While Principle 1 (line 78) identifies that clinical trials should be conducted following ethical principles, the E6(R3) revision stops short of giving the IRB/IEC the responsibility of ensuring specific ethical guardrails during review and approval. Given how much detail is given regarding IRB/IEC responsibilities and operations, it would be wise to include criteria for IRB/REC review and approval of a clinical trial protocol.

In this revision, the ICH GCP E6(R3) guideline has an opportunity to provide guidelines for the minimal requirements of ethical review and approval. We propose including the following list of ethical responsibilities in III.1.1.1.

- The research is socially, culturally, and scientifically valid
- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- The selection of subjects is equitable
- Informed consent will be sought and documented from each prospective subject or the subject's legally authorized representative in a language understandable to the subject or their legally authorized representative, and in accordance with local requirements.

Payment to participants

The IRB/IEC responsibilities include the following language (starting on line 334) regarding payment to participants:

> III.1.1.8: "If the trial participants are compensated for their participation in the trial, the IRB/IEC should review both the amount and method of payment to participants to assure that neither presents problems of coercion or undue influence on the trial participants. Payments to a participant should be prorated and not wholly contingent on

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completion of the trial by the participant. Reasonable reimbursement of participants for travel and lodging is not typically coercive."

Specifically, we suggest the following changes should be made to section III.1.1.8 (line 334, revised language in red font):

- *Suggested language*: If the trial participants and their caregivers are compensated for their participation or support of the participant in the trial, the IRB/IEC should review both the amount and method of payment to participants to assure that neither presents problems of coercion, ~~or~~ undue influence, or burden (e.g. reduction in benefits) on the trial participants. Payments to a participant should be prorated and not wholly contingent on completion of the trial by the participant. Reasonable reimbursement of participants ~~for travel and lodging~~ for eligible out-of-pocket expenses, including, but are not limited to, hotels, ground transportation, meals, and/or childcare/eldercare is expected, not ~~typically~~ coercive, and rarely, if ever, threatens undue influence. The participant should not be worse off financially for his/her participation in a clinical trial.

Of note, the MRCT Center strongly believes reimbursement of participants for out-of-pocket expenses incurred during participation in the trial are never coercive.

Beyond section III.1.1.8, the concept of payment to participants is absent. Sponsor section III.3.14 Insurance/Indemnification/Compensation to Participants and Investigators only states, "The approach to compensating trial participants should comply with applicable regulatory requirements" (line 1495). The ICH GCP guideline has an opportunity to provide a global, harmonized approach to payment by providing additional information and language around payment. Notably, the ICH GCP guideline can formally recognize at least three categories of payment to participants: (1) reimbursement for non-medical expenses (e.g. travel, lodging, childcare/eldercare) incurred by the participant or their caregiver, when needed, as a result of participation, (2) compensation for time and effort related to research participation, and (3) incentive payments to encourage participation, retention, and study completion. These categories of payment are routinely considered and determined in the planning of a clinical trial protocol. The definitions should be included in the ICH GCP Glossary. The Sponsor section should contain general guidance to inform the planning of payment to study participants. The following article provides further information related to fair payment in clinical research.[2]

Informed Consent of Trial Participants

For the past 7 years, the MRCT Center has dedicated tremendous effort to advancing diversity, equity, and inclusion in clinical research. As part of this work, we have recently focused on the

[2] Bierer BE, White SA, Gelinas L, Strauss DH. Fair payment and just benefits to enhance diversity in clinical research. J Clin Transl Sci. 2021 Jul 14;5(1):e159. doi: 10.1017/cts.2021.816. PMID: 34527298; PMCID: PMC8427546.

inclusion of people with disabilities in research. Given this focus, we are sensitive to including language that will increase the inclusion of people with disabilities. We offer the following suggested revisions contained within III.2.8, Investigator, Informed Consent of Trial Participants (revisions provided in red font).

- *Suggested language* III.2.8.1(c)/ line 603: "Varied approaches (e.g., text, images, videos and other interactive methods) may be used in the informed consent process including for providing information to the participant. These communication approaches should be accessible to people with disabilities, in plain language, in translated versions when appropriate, and culturally respectful."
- *New suggested language to be inserted as a separate section before* III.2.8.4 / line 626: The informed consent process should offer and/or respond to supported decision-making in the context of consent.
- *Suggested language* III.2.8.11 / line 681, *Add to the information provided to the participants*: "the trial team and site/s will provide reasonable accommodations for people, and for people with disabilities, upon request by the participant."

Assent

The MRCT Center feels that assent does not receive adequate attention and treatment in the overall E6(R3) draft guideline. We offer the following comments in support of a harmonized approach to assent:

Principle 2 states:

> "Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed" (line 110).

This principle goes on to provide additional analyses of voluntary consent. Assent is not mentioned. We suggest ICH utilize some or all the language from the E11(R1) Clinical Trials in Pediatric Population guideline inserted below:

> *"As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a study (age of assent to be determined by IRB's/IEC's or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent. In all cases, participants should be made aware of their rights to decline." (Section 2.6.3, Consent and Assent)*

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III.2.8.1, IRB/IEC, Informed Consent of Trial Participants (line 587) provides a detailed overview of the informed consent process. We applaud this level of detail and suggest a similar outline of best practices for assent be included in the guidelines.

Transparency of clinical trial results/Return of Results

Returning results to participants allows investigators and sponsors to honor the essential contributions and voluntarism of study participants. Participants may utilize these results to act on a diagnosis or continued treatment. Similarly, posting trials and trial results on publicly available databases advances the transparency of research, contributes to the identification of trials for patients, and theoretically assists in reducing the duplication of trials. Both efforts increase trust in the clinical research enterprise and should no longer be optional. The MRCT Center offers the following revisions as an opportunity to endorse the sharing of trial results and the future use of data.

Principle 9/ line 204, "Clinical trials should generate reliable results":

- *Suggested language*: Clinical trials should generate and communicate reliable results
- Principle 9, and the seven points of analysis, do not extend the responsibility of sponsors or investigators to return aggregate or individual results to study participants. *Suggested language for a new section* 9.1.8: Sponsors and investigators should return study trial results to the participant, unless a scientific, clinical, ethical, or cultural reason exists not to do so. The plan to provide, or the reason not to provide, research results should be submitted to the IRB/IEC, which should review and approve, modify, or reject the plan.

Sponsor, Reports, Clinical Trial/Study Reports

- *Suggested language*: III.3.17.2(c) / line 1806: "~~Consideration~~ Investigators should be given ~~to providing the investigator with~~ information about the final treatment taken by their participants for blinded trials and a brief summary of the overall outcome of the trial. ~~Where this information is provided to participants, the language should be~~ This information should then be provided to participants whenever possible, using language that is non-technical, understandable to a layperson and non-promotional. The sponsor should only supply this information after the trial has been unblinded and all relevant analyses/conclusions have been completed and finalised."
- We appreciate the addition of registration and results reporting in principle 9.7/line 229. This expectation should be reiterated within the Sponsor section. Furthermore, we propose adding a new section to III.3.17.2, Sponsor, Reports, Clinical Trial / Study Reports (line 1794).
    - *New suggested language*: The clinical trial sponsor must register on a publicly accessible and recognised database before initiating the clinical trial. Clinical trial results should be posted on the same public database within a time course set out by regulations and/or policy.

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Post-Trial, Continued Access to Medicines

During the trial design phase, the sponsor is responsible for evaluating whether the product and disease/condition under study may meet criteria for continued access. Continued access is defined as the "continuity of investigational medicine (or comparator), and the needed medical care and health care infrastructure required to appropriately use the investigational medicine to individual participants at the completion of their participation in a clinical trial or at the conclusion of a clinical trial."[3]

A continued access plan should be developed before the initiation of the clinical trial, to determine the circumstances and conditions for which continued access will be considered, including established criteria for the transition of a patient to another mechanism.

Language specific to developing a continued access plan is absent from the E6(R3) revisions. The MRCT Center suggests the following language be included in III.3.1 Sponsor Trial Design (line 926):

- *Suggested new language*: The plan for continued access should be determined before the trial begins and before any individual gives their informed consent. The protocol should delineate continued access plans. The plan should be transparent to potential participants and explained during the informed consent process.

Decentralized Clinical Trials

The MRCT Center recognizes that ICH has announced that Annex 2 will address decentralized clinical trials (DCTs). Over the past few years, and increasing in frequency since COVID-19, there has been a shift in the adoption of decentralized elements in the conduct of clinical trials. Indeed, many, if not most trials now include some decentralized elements. The MRCT Center suggests the following considerations related to DCTs:

- Include a definition of DCT in the Glossary. *New suggested language:* Trials, where some or all trial-related activities occur at locations other than traditional clinical trial sites, such as patient homes, mobile trial units, or local clinics, and data collection, may occur remotely. DCTs are trials executed through telemedicine, mobile technologies, local sites, and mobile healthcare providers.
- Recognize throughout Annex 1 that many trials contain decentralized elements.
- Focus Annex 2 on the unique differences of decentralized clinical trials including (but not limited to) the responsibilities of the investigator and data collection/storage/use.

[3] Aldinger C, Bierer B, Li R, Van Campen L, Barnes M, Bedell E, Brown-Inz A, Gibbs R, Henderson D, Kabacinski C, Letvak L. MRCT Center Post-Trial Responsibilities Framework Continued Access to Investigational Medicines. Guidance Document. Version 1.2, December 2017.

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Appendix B: Clinical Trial Protocol and Protocol Amendments

Below, we provide suggested language to the outline provided in Appendix B to reflect the importance of inclusive study design.

B.2 Background Information:

- Provide concise background on the disease's epidemiology, impact, demographic of affected populations, subgroup variations in safety/efficacy, and available treatments if known.
- Describe the study population(s) considering disease burden, epidemiology, demographics, non-demographic factors (like social determinants of health), and unmet medical needs.
- Provide a clear recruitment plan that outlines the strategies for enlisting diverse participants, including a comprehensive global diversity enrollment strategy.

B.4 Trial Design:

- The study question and design should account for population diversity and potential subgroup variations relevant to the intended product (e.g., ancestry, comorbidities, etc.).
- Incorporating diverse, representative, and inclusive participant and community input is vital for study success. Detail how this input was gathered, how it influenced the study, and how the representativeness of the input was assessed.
- Describe the detailed operational measures that will be implemented to enroll and retain underrepresented populations in the planned study(ies) and the planned use of data to characterize the safety, efficacy, and optimal dosage in these participants when applicable.

B.5 Selection of Participants:

- Include a thorough description of the intended population based on demographic characteristics, disease epidemiology, expected intervention recipients, and other pertinent distributions. This description should encompass demographic elements (e.g., age, sex, gender, race, ethnicity, ancestry) as well as non-demographic factors (e.g., gender identity, social determinants of health, comorbidities, current medications, etc.) in as much detail as possible.
- Ensure all inclusion criteria are scientifically, medically, and ethically sound and account for subgroup differences. Justify exclusion of pediatric populations and adolescents with strong scientific and ethical reasoning. Explain the rationale behind lower and upper age limits, considering less restrictive alternatives when applicable.

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Appendix C: Essential Records for the Conduct of a Clinical Trial

The MRCT Center considered E6(R2), Section 8, Essential Documents for the Conduct of a Clinical Trial, to be one of the most practical and useful sections of the GCP guideline. Notably, sections 8.2 – 8.4 provided stakeholders with specific documents that should be maintained before, during, and after the conduct of the clinical trial. Responsible stakeholders were identified related to who is responsible for maintaining the documents. The use of this section provided sponsors, IRB/IECs, and investigators a roadmap to develop study regulatory binders and study files. We have personal experience in guiding many investigators and clinical research sites around the world with this E6(R2) essential records model.

We applaud the inclusion of section C.3, Essentiality of Trial Records. We note that the previous tables have been replaced with Table 1 – Essential Records for All Trials and Table 2 – Potential Essential Records. While we appreciate the recognition of records required for all trials, we note that all stakeholders will not keep some records and this format may confuse users. We make the following observations:

- For example, Table 1, 1.6 requires "completed signed and dated informed consent forms." IRB/IECs and Sponsors will not maintain these records; the Investigator will.
- Table 1, 1.10 requires 'source records' however and IRB/IEC will not be keeping source records for participants.
- Table 2 – Potential Essential Records, leaves the essentiality open for interpretation.
- Removing the before/during/after leaves the timing up to interpretation.

We recommend the following:

- Maintain Section C.3 Essentiality of Trial Records however, identify a means of categorizing the 28 elements listed.
- Re-introduce tables 8.2-8.4 from the E6(R2) version to the E6(R3) version. The distinction of which stakeholder is responsible for each essential document is helpful.

Additional suggested language revisions:

- Principle 5, 5.1 / line 154, *Suggested language*: "Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, scientists, ethicists, technology experts, trial coordinators, monitors, auditors ~~and~~ statisticians, and patients/trial participants. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s)."
- Sponsor Agreements, III.3.6.8 / line 1006, *Suggested language*: "The sponsor is responsible for assessing the suitability of and selecting the service provider. The service provider must be able to ~~to ensure that they can~~ adequately undertake the activities transferred to them and support the physical, emotional, and environmental safety of participants from diverse backgrounds throughout the trial. The sponsor should provide

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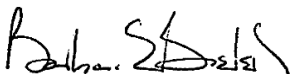
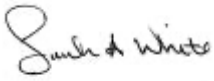
the service providers with the protocol where necessary as well as any other documents required for them to perform their activities."

- Sponsor, Monitoring of Clinical Trials Data, III.3.11.4.5.4 (iii) / line 1383, *Suggested language:* "examine data trends, such as the diversity of the participants providing data, and the range, consistency and variability of data within and across sites;"
- Glossary, Vulnerable Participants (line 2333), *Suggested revisions*: "Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students; subordinate hospital and laboratory personnel; employees of the pharmaceutical industry; members of the armed forces and persons kept in detention. ~~Other~~ Vulnerable participants may also include children, immigrants, individuals of sexual minority, educationally disadvantaged individuals, persons with cognitive or physical disabilities, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent."

Thank you again for the opportunity to comment on the proposed E6(R3) GCP Guideline. We believe that the ICH and FDA has taken an important step to recognize the considerations needed to guide the design and conduct of modern human subjects research. The proposed changes will ensure the rights, safety, and well-being of all trial participants.

Please feel free to contact the MRCT Center (sawhite@bwh.harvard.edu, bbierer@bwh.harvard.edu, or mark.barnes@ropesgray.com) if we can be helpful or if you wish to discuss.

Respectfully submitted,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