POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

INDs: Review of Informed Consent Documents

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PURPOSE

- This Manual of Policies and Procedures (MAPP) describes: (1) when an informed consent document (ICD) submitted under an investigational new drug application (IND) should be reviewed; (2) when the Center for Drug Evaluation and Research (CDER) should request that an ICD be submitted to an IND; and (3) procedures for reviewing an ICD.

- This MAPP does not address consent for treatment INDs or exception from informed consent requirements for emergency research. The review of ICDs for those two regulatory scenarios is covered by procedures described in CDER MAPP 6030.6, *INDs: Processing Treatment INDs and Treatment Protocols* and CDER MAPP 6030.8, *INDs: Exception from Informed Consent Requirements for Emergency Research,* respectively.[1] This MAPP also does not address exceptions from informed consent requirements per 21 CFR 50.22 – *Exception from informed consent requirements for minimal risk clinical investigations* and 21 CFR 50.23 – *Exception from general requirements*.

[1] For the current version of a CDER MAPP, refer to the website *CDER Manual of Policies & Procedures* at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

BACKGROUND

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505(i)(4) provides that each IND is conditioned on the sponsor requiring that the clinical investigator: (1) inform human subjects or their legally authorized representatives (LAR) that drugs are being used for investigational purposes; and (2) obtain consent of the human subjects or their LAR, except where it is not feasible or is contrary to the human subjects' best interests.

- Except as described in 21 CFR 50.22 – 24, no investigator may involve a human as a subject in research involving an investigational product unless the investigator has obtained the legally effective informed consent of the subject or the subject's LAR.[2]

- The institutional review board (IRB) reviews, has the authority to approve, require modifications in (to secure approval) or disapprove all FDA regulated research activities.[3] Additionally, the IRB must require that information given to subjects as part of informed consent be in accordance with 21 CFR 50.25 and may require additional information be provided subjects.[4] CDER's review of the ICD does not substitute for the responsibility or authority of the IRB. However, CDER retains the authority to review and require changes to the ICD.

- The IRB is responsible for reviewing the ICD for all clinical investigations under their jurisdiction. In addition to IRB review, there are situations where CDER review of an ICD is necessary to determine if a clinical investigation may safely proceed under FDA's IND regulations at 21 CFR 312. The IND regulations do not require routine submission of ICDs to CDER; however, CDER can request submission of the ICD for review to determine whether the ICD ensures that human subjects are provided sufficient information to consider whether or not to participate in the clinical investigation.[5]

POLICY

- If a sponsor does not submit an ICD as part of its IND submission, the Office of New Drugs (OND) Clinical review division may request and review the ICD at any time. The request may reference 21 CFR 312.23(a)(11), which states that if requested by the Food and Drug Administration (FDA), the sponsor must submit *"…any other relevant information needed for review of the application."* FDA

[2] Refer to 21 CFR 50.20.
[3] Refer to 21 CFR 56.109(a).
[4] Refer to 21 CFR 56.109(b.)
[5] Refer to 21 CFR 312.23(a)(11).

review of the ICD is strongly recommended when the proposed investigational use raises a concern. For example:

- Toxicities identified in nonclinical studies submitted to support administration of an investigational product in humans that may predict serious adverse effects in humans.

- A known clinically meaningful, serious adverse reaction associated with the investigational product (e.g., due to the active ingredient(s) or excipients) or the drug/biological product class to which the active ingredient(s) belongs.

- The study population could be considered vulnerable.[6]

- The study design is unusual for the therapeutic class.

- The clinical investigation has significant potential for serious risk to human subjects.

- The clinical investigation is a postmarketing study or clinical trial required under section 505(o)(3) of the FD&C Act to assess a serious risk related to the use of the product.

- The clinical investigation involves asking subjects to forego or delay effective treatment that is known to decrease long-term mortality or irreversible morbidity.

- CDER has other confidential or proprietary information not available to an IRB or sponsor that affects the assessment of whether the ICD adequately addresses risks.

- The IND Review Team will focus their review of the ICD on the:[7]

  - Statement that the study involves research.

  - Explanation of the purposes of the research and expected duration of the subject's participation.

  - Description of the procedures to be followed and identification of any experimental procedures.

  - Description of any reasonably foreseeable risks or discomforts to the subject.

[6] FDA regulations do not specifically define *vulnerable*. As a general matter, subjects may be considered vulnerable when, among other things, they have an increased susceptibility to undue influence or coercion. Examples of vulnerable categories of subjects include children, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.
[7] Refer to 21 CFR 50.25(a)(1 – 4).

- Description of any benefits to the subject or to others that may be reasonably expected from research.

- Disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject.

- Written information in the consent form to help ensure it is in a language and at a level understandable to the prospective subject or the LAR.[8]

- The IND Review Team will request a review by the Office of Scientific Investigations (OSI) in CDER's Office of Compliance (OC), if there are questions about whether the ICD meets the requirements outlined in 21 CFR 50.

- The OND Clinical reviewer will request a review by the relevant Ethics team if there are ethical concerns about the ICD. For research involving adults, contact the Adults Ethics team in the Office of Clinical Policy (OCLP) in the Office of the Chief Medical Officer (OCMO). For research involving children, contact the Pediatric Ethics team in the Office of Pediatric Therapeutics (OPT) in the Office of the Chief Medical Officer (OCMO).

- After reviewing the ICD, if the IND Review Team (and as applicable, OSI, and/or an FDA ethicist) have concerns about the ICD, they should provide comments to the sponsor in writing.

- If the IND Review Team (and as applicable OSI, and/or an FDA ethicist) find an ICD to be misleading, inaccurate, or noncompliant with applicable regulations in 21 CFR 50, the review team must convey required changes to the sponsor in writing as soon as possible. Promptly addressing these changes may avoid the imposition of a clinical hold.

- If the IND review team determines that an ICD's deficiencies are such that subjects do not have the information necessary to make an informed consent decision, the division should place the IND on clinical hold under 21 CFR 312.42(b)(i) if *"…human subjects are or would be exposed to an unreasonable and significant risk of illness or injury."* The OND Clinical review division will attempt to discuss and satisfactorily resolve any deficiencies with the sponsor before putting the IND on hold. If the deficiencies cannot be resolved, the division will place on the IND on hold. Comments regarding continued deficiencies with the ICD will be conveyed to the sponsor in writing within 30 calendar days of the hold action. The sponsor is expected to submit a revised ICD for FDA review in their complete response to clinical hold to determine if the concerns have been adequately addressed.[9]

[8] Refer to 21 CFR 50.20.
[9] Refer to 21 CFR 312.42(e) and CDER MAPP 6030.1, *IND Clinical Holds*.

- For multicenter trials with local IRB review of the ICD (i.e., for which the content of the ICD may vary somewhat from site to site), CDER will advise the sponsor to revise the ICD for each site to address CDER comments on safety issues or issues of regulatory noncompliance.

RESPONSIBILITIES

IND Review Team:

- If needed for review of the application, request submission of the ICD if it has not been included with the IND.[10]

- Review the ICD as described in the POLICY section. When indicated, the appropriate discipline will contact Office of Regulatory Operations (ORO) staff to obtain additional collaborative consultation with OSI.

OND Clinical Reviewers:

- Review the ICD as described in the POLICY section. When indicated, inform ORO staff to contact the applicable FDA Ethics Review Team for an ethics review.

OND/Office of Regulatory Operations (ORO) Project Management Staff:

- Submit consultation requests, including all relevant documentation (e.g., ICD, protocol, investigator's brochure), to OSI or the applicable FDA Ethics Review Team, as appropriate.

- Provide the OSI and the FDA Ethics Review Team findings to the IND Review Team.

- Communicate inquiries to the sponsor and inform the IND Review Team of sponsor responses.

OC/Office of Scientific Investigations:

- At the request of the IND Review Team, review the ICD for compliance with applicable requirements of 21 CFR 50, and forward written comments on the ICD to ORO staff within 10 business days of receiving the review request, which will include all relevant documents.

[10] Refer to 21 CFR 312.23(a)(11).

OCLP/FDA Ethics Review Team (Adult and/or Pediatric Ethics Teams):

- If the OND Clinical reviewer requests an ethics review:

  – Upon receipt of an ethics review request, the ethicist reviews the ICD and other study-related documents to evaluate the ethical acceptability of the ICD; and will address any questions posed by the OND Clinical reviewer and that are identified during the ethics review. In conducting this review, the ethicist will consider existing FDA policies and the regulatory requirements in 21 CFR 50, 56 and 312.

  – The ethicist completes a written review addressing the ethics of the ICD and its conformance with applicable regulations and identifying other concerns.

  – The ethicist archives the written review in a timely manner in the appropriate CDER Electronic Records Keeping System (ERKS).

  – Ideally, the FDA Ethics Review Team will be provided at least 10 business days to complete their review. If it is not possible to provide the Ethics Review Team a 10 business day window, contact the relevant Ethics Review Team directly so that the need for the review and the deliverable date can be discussed.

PROCEDURES

1. If requesting a review from OSI or an FDA ethicist, ORO staff forwards copies of the ICD, the protocol, investigators brochure, and other relevant supporting documentation as applicable with the request for review. Review requests should include specific questions or concerns the IND Review Team has with the ICD.

2. When IND Review Team has concerns that the ICD does not meet applicable requirements in 21 CFR 50, ORO staff submit the review request to OSI via the appropriate ERKS. OSI responds to requests within 10 business days of receiving the request, which will include all relevant documents.

3. When the OND Clinical reviewer has ethical concerns related to the ICD, ORO staff will submit a request to the appropriate FDA ethicist team for adults or pediatrics, or both, in the appropriate ERKS for a specific study population and include the due date for a response. ORO staff should request a response through the appropriate ERKS with a due date.

4. The IND Review Team will review all comments provided by OSI and the FDA Ethics Review Team. The OND Clinical review division will determine which comments should be conveyed to the sponsor. Comments determined by OND Clinical review division not to be conveyed to sponsor will be discussed with OSI

or the FDA Ethics Review Team. This discussion should occur prior to the final decision made by the OND Clinical review division director (or designee).

5. OND Clinical reviewer will document any ICD changes as part of the IND clinical review in the appropriate ERKS.

REFERENCES

- Federal Food Drug and Cosmetic Act (FD&C Act), Sections 505(i)(4) and 505(o)(3).
- 21 CFR 50 – *Protection of Human Subjects*.
- 21 CFR 56 – *Institutional Review Boards*.
- 21 CFR 312 – *Investigational New Drug Application*.
- Draft Guidance for Industry: *Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards*.[11]
- Guidance for Industry: *Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors*.
- CDER MAPP 7600.11, *CDER Electronic Record Keeping Systems*.
- CDER MAPP 6030.1, *IND Clinical Holds*.
- CDER MAPP 6030.8, *INDs: Exception from Informed Consent Requirements for Emergency Research*.
- CDER MAPP 6030.6, *INDs: Processing Treatment INDs and Treatment Protocols*.

DEFINITIONS

- **FDA Ethicist**: An FDA expert in biomedical ethics who addresses and analyzes the ethical implications of research in the areas of biomedical sciences and public health and makes recommendations accordingly.

- **IND Review Team**: The team composed of members of different disciplines (e.g., the clinical reviewer, ORO staff, product quality assessor, clinical pharmacologist, microbiologist, biostatistician, and other disciplines as appropriate) who review and make recommendations concerning the IND.

- **Informed Consent**: Informed consent is a process that involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, providing adequate opportunity

[11] For the current version of an FDA guidance, refer to the website *Search for FDA Guidance Documents* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

for the potential subject to consider whether or not to participate, obtaining the potential subject's voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires.[12]

- **Informed Consent Document (ICD)**: The ICD is a written document that provides the study subject with information essential to making an informed decision about participating in a clinical investigation. The signature of the study subject or the subject's legally authorized representative on the ICD indicates the intent of the subject or the subject's legally authorized representative to give informed consent. The term *consent form* is also used to refer to the ICD.[13]

- **Institutional Review Board (IRB)**: Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to ensure the protection of the rights and welfare of the human subjects.[14]

- **Legally Authorized Representative (LAR)**: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.[15]

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
11/13/2002	Initial	N/A
05/02/2014	Revision 1	1. Corrected designation 'Office of Scientific Investigation.' 2. Changed Background section.

[12] Refer to 21 CFR 50.20 – *General requirements for informed consent* and the guidance for industry: *Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors* for additional information.
[13] Refer to 21 CFR 50.25 – *Elements of informed consent* and 21 CFR 50.27 – *Documentation of informed consent*.
[14] Refer to 21 CFR 56.102(g).
[15] Refer to 21 CFR 50.3(l).

		3. Changed Policy section, clarifying situations when ICDs should be reviewed. 4. Change in Responsibilities and Procedures sections, clarifying instructions for requesting OSI and ethics consults. 5. Added ethics consultations procedures. 6. Added references.
7/17/2025	Revision 2	Updated to align with current OND organizational structure, applicable user fee agreement (UFA) commitments, and CDER best practices and workflow procedures.