OFFICE OF NEW DRUGS

INDs: Review of Informed Consent Documents

CONTENTS

PURPOSE

- This MAPP is for medical officers and project managers. It 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, when necessary.

BACKGROUND

- The Federal Food, Drug, and Cosmetic Act states that an IND is conditioned upon the sponsor requiring that the investigator (1) inform human subjects about the investigational purposes of the drug use and (2) obtain consent of the human subjects or their representatives, except where it is infeasible or contrary to the human subjects' best interests (section 505(i)(4)).

- Except as described in 21 CFR 50.23 and 50.24, no clinical investigator may involve a human being as a subject in research involving an investigational drug unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative (21 CFR 50.20).

- **It is the responsibility of the institutional review board (IRB)** to ensure that information given to subjects as part of the informed consent process contains the elements identified in 21 CFR 50.25 and meets the requirements of 21 CFR 50.20. The IRB can require that information in addition to that specifically mentioned in section 50.25 be given to the subjects when, in the judgment of the IRB, the information would meaningfully add to the protection of the rights and welfare of subjects (21 CFR part 56).

- Because the IRB is responsible for reviewing ICDs for all clinical investigations under its jurisdiction, the IND regulations do not require that ICDs be routinely submitted to CDER. There are situations in which review of an ICD by CDER in addition to IRB review is particularly important to determine whether a clinical investigation may safely proceed under 21 CFR part 312 (see **POLICY** below). In these situations, CDER will review the ICD if the sponsor has submitted it as part of their IND submission. If the ICD has not been submitted, CDER will request that the sponsor submit it for review.

- At the request of the review divisions, the Human Subject Protection (HSP) Team, Division of Scientific Investigations (DSI), will review ICDs submitted to INDs for compliance with the requirements of 21 CFR part 50.

REFERENCES

- IND Process and Review Procedures, MAPP 6030.1
- 21 CFR part 50, Protection of Human Subjects
- 21 CFR part 56, Institutional Review Boards

DEFINITIONS

- **Informed Consent**: Informed consent is the process by which an investigator provides a potential study subject sufficient information about the nature and extent of the planned research, study procedures, potential risks and benefits, alternative therapeutic options, confidentiality, and other pertinent issues (see 21 CFR 50.25) to enable the subject to make an informed decision about whether to participate in the trial. The process may include recruitment materials, written materials, question and answer sessions, and measurements of subject understanding (i.e., the process of informed consent may involve more than just the informed consent document).

- **Informed Consent Document (ICD)**: The ICD is a written form 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.

- **Institutional Review Board (IRB)**: A board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic reviews of biomedical research involving human subjects.

- **Human Subjects Protection (HSP) Team**: The HSP Team within the Division of Scientific Investigations (DSI), Office of Medical Policy, is responsible for assigning, participating in (as necessary), and evaluating inspections of IRBs participating in

clinical drug studies. The HSP Team may conduct reviews of informed consent documents as part of their oversight of human subject protection.

POLICY

- ICD review is at the discretion of the review division but, in most cases, ICDs should be reviewed as part of the review of an IND submission when review of the proposed investigational use raises a particular concern about the adequacy of informed consent. For example, review of an ICD is warranted when:

  - Unusual toxicity is associated with the study drug
  - The study population is particularly vulnerable
  - The study design is unusual for the therapeutic class
  - CDER is in a better position than the IRB to assess whether the ICD adequately addresses a particular concern based on proprietary data

  In these situations, the review division should assess the adequacy of the ICD in addressing any safety issues or matters of study design and the elements identified in 21 CFR 50.25. If the division has specific concerns about the ICD's compliance with 21 CFR part 50, it should forward copies of the ICD, the protocol, and other relevant supporting documentation to DSI with a request for consultative review.

- In addition, in the following circumstances, CDER review of the ICD is always recommended:

  1. Treatment INDs and Treatment Protocols (21 CFR 312.34 and 312.35). In this situation, review of the ICD by CDER as well as the IRB may be particularly important (a) because of the vulnerable nature of the patient population (patients with serious or life-threatening conditions) and (b) to ensure that subjects are not misled about what is known about the safety and effectiveness of the investigational drug. When an ICD for a treatment IND or treatment protocol is reviewed, the review division should determine whether the ICD contains sufficient information for a study subject or the subject's legally authorized representative to make an informed decision, and whether the ICD is medically and scientifically accurate. Copies of the ICD, protocol, and any other supportive information should also be forwarded to DSI for review.

  2. Exception from Informed Consent Requirements for Emergency Research (21 CFR 50.24). In this situation, review of the ICD by CDER as well as the IRB may be particularly important (a) because of the vulnerable patient populations studied under emergency research exemptions and heightened ethical concerns associated with research in these populations and (b) to ensure that subjects (or their legally authorized representatives) are not misled about what is known about the safety and effectiveness of the drug. When an ICD is reviewed, the review division will determine whether the ICD contains sufficient information for a study subject or the subject's legally authorized representative to make an informed decision, and whether the ICD is medically and scientifically accurate.

Copies of the ICD, protocol, and any other supportive information should also be forwarded to DSI for review.

- If a sponsor has submitted an ICD as part of its IND submission, but the protocol does not fall under any of the situations identified above, it may still be useful to review the ICD to rule out significant deficiencies.

- If a sponsor has not submitted an ICD as part of its IND submission, but the protocol falls under one of the situations described above, the review division should request that the sponsor submit an ICD. The request should reference 21 CFR 312.23(a)(11), which states that if requested by the Agency, the sponsor must submit "… any other relevant information needed for review of the application."

- An ICD requested by CDER should be reviewed.

- Ordinarily, CDER comments (review division or DSI) on the content of an ICD should be advisory. They need not specifically prescribe how the sponsor should address the comments, and the investigation need not be put on hold pending submission of a revised ICD.

- In some situations, the review division or DSI may find an ICD to be misleading, inaccurate, or incomplete in a way that raises a significant safety concern for potential study subjects and requires that specified revisions be made to address the concern before a trial can proceed. In such cases, the review division may place the IND on clinical hold until an acceptable revision of the ICD is received (see MAPP 6030.1, IND Process and Review Procedures, and 21 CFR 312.42, Clinical Holds and Requests for Modification), or may discuss specific modifications with the sponsor to avoid a clinical hold.

- 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), the sponsor should be advised to ensure that the ICD for each center is revised to address CDER comments on safety issues.

RESPONSIBILITIES and PROCEDURES

IND Review Team will:

- Request submission of the ICD if it has not been submitted with the IND when one of the circumstances listed in the **POLICY** section above applies.

- Review the ICD as described in the **POLICY** section. When indicated, consult DSI (see **POLICY** section).

- Review the comments provided by DSI to determine which comments should be conveyed to the sponsor. A determination not to convey a DSI comment to the sponsor should be discussed with DSI. This discussion should take place before a final decision is made not to convey the comment to the sponsor.

Project Management Staff will:

- Forward copies of the ICD, protocol, and related information (e.g., Investigator's Brochure) to DSI (HFD-45), for review when (see **POLICY** section):
    - The submission is either a treatment IND, treatment protocol, or emergency research IND
    - The review division has concerns about whether the ICD meets the requirements of 21 CFR part 50
- Ensure that appropriate comments on the ICD, as determined by the review team, are provided to the sponsor.

Human Subject Protection (HSP) Team, Division of Scientific Investigations will:

- Evaluate informed consent documents for conformance with 21 CFR part 50.
- Forward comments on the ICD to the project manager within 7 calendar days of receipt by the HSP Team. The HSP Team may respond by memorandum or other written form of communication (e.g., e-mail or fax).

EFFECTIVE DATE

This MAPP is effective upon date of publication.