OFFICE OF NEW DRUGS

INDs: Exception from Informed Consent Requirements for Emergency Research

CONTENTS

PURPOSE

- This MAPP describes the procedures for processing an investigational new drug application (IND) for emergency research in which the clinical investigation described includes a request, pursuant to 21 CFR 50.24, for an exception from the requirement to obtain informed consent from all study subjects.

BACKGROUND

- Research conducted under § 50.24 involves a particularly vulnerable population: persons with life-threatening conditions who can neither give informed consent nor actively refuse enrollment. This lack of autonomy creates a special need for FDA, sponsors, institutional review boards (IRBs), and clinical investigators to work closely together to ensure that the interests of this vulnerable population of subjects are protected. The regulations for emergency research therefore contain specific human subject protection requirements — for example, consultation with the community about the planned study and disclosure to the community about the study results — in addition to the requirements for all clinical studies conducted under an IND.

- Each protocol for a clinical investigation for emergency research that includes an exception from informed consent under § 50.24 must be submitted in a unique IND and be clearly identified as including subjects who are unable to give their informed consent. Protocols for clinical investigations under this section may not be submitted as protocol amendments to existing INDs under 21 CFR 312.30(a). The sponsor must submit a separate IND for each additional protocol involving this exception, even if an IND for the same drug product or an IND involving § 50.24 for the same drug product already exists (§ 50.24(d)).

- INDs for emergency research conducted under § 50.24 must be submitted, reviewed, and granted permission to proceed in writing by FDA prior to subject enrollment and must be in conformance with the content and format requirements for an IND. (See 21 CFR 312.2(b)(6) and 312.23, generally.) This MAPP does ***not*** apply to emergency treatment (open-label) of individual patients with investigational drugs without informed consent by physicians carrying out medical care in a life-threatening situation as provided under 21 CFR 50.23 or to an emergency situation that does not allow time for submission of an IND as provided under 21 CFR 312.36 (i.e., "emergency" INDs).

- Although these studies involve an exception from informed consent under § 50.24, each site is required, nevertheless, to develop an informed consent document and procedures for attempting to find and obtain informed consent from a subject's legally authorized representative. (See § 50.24(a)(6) and (b).)

  The clinical investigator will generally ***not*** be able to obtain informed consent from each study subject (because of the subject's condition) or from the subject's legally authorized representative prior to enrolling the subject in the study (because the representative cannot be found in time). In some instances, however, the clinical investigator may be able to do so. In addition, a subject may later regain consciousness, or the clinical investigator may eventually locate the subject's legally authorized representative.

  The regulations require the clinical investigator to (1) inform the subject or the subject's legally authorized representative, at the earliest opportunity, about the subject's inclusion in the study and (2) provide an opportunity for the subject or the legally authorized representative to withdraw the subject from the study or sign a consent form agreeing to the subject's continued participation in the study. Thus, the informed consent document and procedures need to be developed and available so that they can be used where feasible.

- If necessary, FDA may place a proposed or ongoing emergency research investigation (or study site) involving § 50.24 on clinical hold (1) if any of the conditions in 21 CFR 312.42(b)(1) or (b)(2) apply ***or*** (2) if the pertinent criteria in § 50.24 for such an investigation to begin or continue are not met (21 CFR 312.42(b)(5)).

  Please refer to MAPP 6030.1, IND Process and Review Procedures, and 21 CFR 312.42, Clinical Holds and Requests for Modification, for more details on clinical hold procedures.

REFERENCES

- 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research

- 21 CFR 56.109(g), IRB Review of Research

- 21 CFR 312.20(c), Requirement for an IND
- 21 CFR 312.23(f), IND Content and Format
- 21 CFR 312.30, Protocol Amendments
- 21 CFR 312.42(b)(5), Clinical Holds and Requests for Modification
- 21 CFR 312.54, Emergency Research Under § 50.24 of This Chapter
- 21 CFR 312.81(a), Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses
- *Draft Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research* (March 2000), available on FDA's Web site at http://www.fda.gov/ora/compliance_ref/bimo/emrfinal.pdf
- Final rule, "Protection of Human Subjects; Informed Consent," 61 FR 51948-51531 (October 2, 1996)
- Proposed rule, "Protection of Human Subjects; Informed Consent," 60 FR 49086-49103 (September 21, 1995)
- MAPP 4151.1, Resolution of Disputes: Roles of Reviewers, Supervisors, and Management; Documenting Views and Findings and Resolving Differences
- MAPP 4512.1, Formal Meetings Between CDER and CDER's External Constituents
- MAPP 6030.1, IND Process and Review Procedures
- MAPP 6030.2, INDs: Review of Informed Consent Documents

DEFINITIONS

- **Community consultation:** Community consultation means providing the opportunity for discussions with, and soliciting opinions from, the community(ies) in which the study will take place and from which the study subjects will be drawn. These communities may not always be the same; when they are not the same, both communities should be consulted.
- **Emergency research:** A planned clinical investigation that is subject to FDA authorization in advance and involves subject(s) who are experiencing immediately life-threatening conditions for which available treatments are unproven or unsatisfactory. (Informed consent will not be obtained for most subjects, due to the subjects' medical condition and because it may not be possible to find a legally authorized representative to provide informed consent for the subject during the therapeutic window identified in the study protocol.)

- **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.

- **Legally authorized representative:** An individual or judicial or other body authorized under applicable law to give informed consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (21 CFR 50.3(l)). IRBs and clinical investigators should familiarize themselves with applicable state and local statutes and regulations pertaining to the definition of a legally authorized representative.

- **Life-threatening:** Diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted (see 21 CFR 312.81(a)). Section 50.24 applies only to clinical research involving life-threatening ***emergency*** situations. An exception from informed consent requirements under § 50.24 is not intended to apply to persons who are not in an emergency situation (e.g., in a long-term coma) or to subjects for whom prospective informed consent is feasible.

- **Public disclosure:** Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware that the study will be conducted and, later, that the communities and scientific researchers are aware of the study's results.

- **Therapeutic window:** The therapeutic window is the time period, based on available scientific evidence, during which administration of the test article might reasonably produce a demonstrable clinical effect.

  The therapeutic window cannot be known until the relation of time of treatment to treatment outcome is formally studied. Nevertheless, the sponsor must use available data (e.g., pathophysiologic data, animal data) to identify the therapeutic window during which administration of the test article to study subjects should be initiated (§ 50.24(a)(5)). The therapeutic window should be specified in the study protocol, as well as the amount of time to be devoted to seeking informed consent.

POLICY

- The Review Divisions (Offices of Drug Evaluation I-V) within the Office of New Drugs (OND) will refer ***all*** INDs involving an exception from informed consent requirements under § 50.24 to the Division of Scientific Investigations (DSI, HFD-45), Office of Medical Policy (OMP), for review. DSI will review the following for appropriateness and conformance with applicable regulations:

- the plans for consultation with, and public disclosure to, the community or communities in which the clinical investigation will take place and from which the subjects will be drawn;
- the procedures for informed consent; and
- the informed consent document (ICD).

- The plans for community consultation and public disclosure and procedures for informed consent should be submitted to the IND. Although the IND regulations do not require submission of informed consent documents, CDER will request a copy of the informed consent document for applications involving an exception under § 50.24.

- The decision to place on clinical hold a study that involves an exception from the requirements for informed consent is made by the review division after evaluating the scientific-medical aspects of a study and after considering the comments of DSI.

  In some situations, the review division or DSI may find an informed consent document 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 informed consent document is received (see MAPP 6030.1, IND Process and Review Procedures, and 21 CFR 312.42, Clinical Holds and Requests for Modification) or discuss specific modifications with the sponsor to avoid a clinical hold.

  In case of appeal of a clinical hold based on DSI's review, OND will consult with OMP/DSI.

- Because participation in the study must hold out the prospect of direct benefit to study subjects, Phase 1 safety studies are not appropriate candidates for this exception.

RESPONSIBILITIES

The **Review Divisions (Offices of Drug Evaluation I-V)** within the **Office of New Drugs, HFD-20)** are responsible for

- Processing and reviewing IND submissions that propose exceptions from the informed consent requirements to determine if the submission is complete and meets the requirements in § 50.24. Note: Requirements in § 50.24(a)(6), (a)(7), and (b) will be reviewed by DSI.

- Evaluating the IND submissions for scientific-medical appropriateness, including whether the research study protocol will obtain useful and necessary data about the safety and effectiveness of the test article being evaluated. For example:

- Does the information derived from animal and preclinical studies and related evidence support a conclusion that the study holds out the prospect for direct benefit to subjects in the study?

- Could the data be obtained from a study that would not require an exception from the informed consent requirements?

- Is the identified therapeutic window reasonable, based upon the available scientific evidence?

- Has the sponsor provided a sound rationale for the trial design, particularly if there is a group of subjects that will be given neither a standard treatment (if any) nor the treatment under study?

- Requesting a copy of the informed consent document, if it was not submitted.

- Forwarding consult requests to DSI to review the plans for community consultation and public disclosure, the informed consent procedures, and the informed consent document.

- Considering the comments made by DSI regarding the plans for community consultation and public disclosure, the informed consent procedures, and the informed consent document.

- Responding to the sponsor as to whether the study may proceed or has been placed on clinical hold.

The **Division of Scientific Investigations, Office of Medical Policy (HFD-45),** is responsible for:

- Reviewing the community consultation and public disclosure plans, informed consent procedures, and proposed informed consent document to ensure that the requirements of § 50.24 are met.

- Providing comments to the review division about whether the plans for community consultation and public disclosure, the informed consent procedures, and the informed consent document meet the requirements of § 50.24.

PROCEDURES

The **Project Management Staff of the Review Division**

- Prepares and issues an acknowledgment letter for an IND submitted pursuant to 21 CFR 312.20(c). If more than one protocol is included in the IND, or if the protocol is submitted to an already active IND, requests that the sponsor resubmit a separate IND for each additional emergency research protocol.

- Notifies the Associate Director for Human Subject Protection (HSP) and the HSP Team Leader, DSI, that the Review Division has received an IND containing a request for an exception from informed consent requirements for emergency research under § 50.24. Notification may be done by e-mail, telephone, or fax.

- Requests a copy of the informed consent document from the sponsor, if it has not been submitted.

- Within seven (7) calendar days of receipt by FDA, forwards a consult request, by fax or e-mail, to DSI (HFD-45), Attention: Associate Director for HSP or HSP Team Leader, with a copy of the IND.

- Prepares and issues a letter (study may proceed or clinical hold, as appropriate) to the sponsor **no later than 30 days after receipt of the IND by FDA**, reflecting the Review Division's scientific-medical evaluation of the study and noting any deficiencies or problems identified in DSI's written review of the plans for consultation and public disclosure, the informed consent document, and the informed consent procedures.

- Ensures that the sponsor receives a copy of the action letter no later than 30 days after receipt of the IND by FDA, which may require sending a copy by fax or e-mail. Forwards the hard copy by regular mail.

- Consults DSI on any resubmission after clinical hold when the hold is based on comments from DSI.

- Consults with DSI on a submission/report from the sponsor of any determination by any IRB that it cannot approve the emergency research due to failure to meet the criteria in the exception under § 50.24(a) or because of other relevant ethical concerns.

- Consults with DSI on a submission providing copies of information publicly disclosed by the IRBs (§ 50.24(a)(7)(ii) and (a)(7)(iii)).

- Ensures, by contact with the sponsor, that the sponsor has submitted a copy of the information that was publicly disclosed both to the IND file and to the Public Docket, Number 95S-0158, maintained by the Dockets Management Branch, HFA-305, 5630 Fishers Lane, Room 1061, Rockville, MD, 20857, as required by 21 CFR 312.54(a).

The Associate Director for Human Subject Protection, Division of Scientific Investigations (HFD-45)/HSP Team Leader:

- Assigns the plans for consultation and public disclosure, and informed consent procedures and document to a member of the HSP team for review.

- Within ten (10) calendar days of receipt of the IND consult, signs in DFS the completed review of the plans for consultation and public disclosure, informed consent document and procedures. Notifies the Project Manager in the Review Division and forwards the review via DFS. In the absence of the Associate Director for HSP, review may be endorsed by the Director or the Deputy Director, DSI.

The HSP Reviewer, HSP Team, DSI:

- Prepares a written review indicating agreement or nonagreement with (1) the plans for consultation with and public disclosure to the communities in which the clinical investigation will take place and from which the subjects will be drawn and (2) the informed consent procedures and document for appropriateness and conformance with the regulations

- Returns through his or her supervisor to the Project Manager in the Review Division, within ten (10) calendar days of receipt of the IND consult request, a written review of the plans for consultation and public disclosure, and the informed consent procedures and document. Checks in a copy of DSI's review to DFS. Gives a copy of DSI's review to the Director, HFD-45. Copies should also be placed in DSI's file of § 50.24 requests and filed for reference purposes in the jacket of the IRB that reviewed and approved the study.

The **Director, Office of New Drugs (HFD-20), and the Director, Office of Medical Policy (HFD-40), will**

- Resolve any conflict between DSI and OND regarding placing a study on clinical hold.

- Resolve appeals from the sponsor related to placing a study on clinical hold.

EFFECTIVE DATE

This MAPP is effective upon date of publication.