KING & SPALDING

Client Alert

FDA & Life Sciences Practice Group

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FDA Updates Manual on Review of INDs Seeking Exception from Informed Consent for Emergency Research under 21 C.F.R. § 50.24

On November 17, 2014, the U.S. Food and Drug Administration (FDA) published a revised version of its internal review procedures and policies for Investigational New Drug applications (INDs) that implicate the exception to the requirement to obtain informed consent from research subjects for emergency research. Specifically, the Agency updated section 6030.8, *INDs: Exception from Informed Consent Requirements for Emergency Research*, of its Manual of Policies and Procedures (MAPP) for the Center for Drug Evaluation and Research (CDER) to place a greater emphasis on obtaining consent and to include a detailed checklist for Agency review components.[1] Replacing the 2003 version, the additional specifications provided by the new version to sponsors of IND applications, as well as FDA personnel, comes at an opportune time. This exception from informed consent for the use of investigational drugs in emergency research could be sought for public health situations where potential research subjects are incapacitated, in a life-threatening clinical situation, and unable to immediately give consent (e.g., community outbreaks of Ebola virus infection).

Background

The exception from informed consent for emergency research, provided under 21 C.F.R. § 50.24, is intended to ensure stringent protections in circumstances where, due to the emergency nature of medical care under research, subjects who are to be enrolled in an IND or Investigational Device Exemption (IDE) protocol are anticipated to be incapacitated and largely unable to provide informed consent. It is typically used to enable research of investigational drugs and medical devices regulated by FDA on conditions such as traumatic brain injury or stroke.

This provision, applying to a unique, prospectively obtained IND or IDE for a systematic collection of scientific data about a test article for emergency research, is distinct from the treatment of an *individual* patient with an investigational drug or medical device by a physician under 21 C.F.R. § 50.23, where immediate use of the test article is, in the investigator's opinion, required to preserve the subject's life, and among other requirements, the subject is unable to provide consent and there is insufficient time to obtain consent from the subject's legal representative. The exception provided under 21 C.F.R. § 50.24 is also distinct from the IND provisions for expanded access to investigational drugs for treatment use, including

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emergency treatment for an individual patient as provided under 21 C.F.R. § 312.310(d).

To our knowledge, the Center for Devices and Radiological Health (CDRH) has not implemented an update to its internal processes similar to the revision of this MAPP, which is only applicable to CDER.

Section 50.24 provides detailed requirements for approval of the exception from informed consent requirements for emergency research. In order for an exception from informed consent to be permitted, an institutional review board (IRB) must find and document each of the following:

(1) The proposed human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of scientific evidence – which may include evidence obtained through randomized placebo-controlled investigations – is necessary to determine the safety and effectiveness of the proposed intervention;

(2) It is not feasible to obtain informed consent due to the subject's medical condition, because the intervention must be administered before consent from a legally authorized representative (LAR) can be obtained, and there is no reasonable way to prospectively identify those individuals likely to become eligible to participate in the study;

(3) Participants are likely to benefit directly from the intervention, considering non-clinical data, and the risks of the intervention are reasonable in relation to those associated with the medical condition at issue and treatment alternatives;

(4) The investigation could not practicably be conducted without a waiver;

(5) The investigator commits to attempting to contact a LAR to obtain consent within a prospectively defined therapeutic window before proceeding and documents those efforts for later IRB review;

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document for use in situations where the subject or LAR is able to consent prior to treatment or when they become able to do so; and

(7) Additional protections for the rights and welfare of subjects are provided, including community consultation, public disclosure prior to initiating the study, disclosure of results after the study has been completed, establishment of an independent data monitoring committee to oversee the investigation, and commitment to attempt to contact a subject's family member to provide an opportunity to object to participation, if a LAR is not reasonably available.[2]

In addition, the IRB must ensure that procedures are in place to inform the subject, the subject's LAR, or, if a LAR is not reasonably available, a family member of the subject at the earliest feasible opportunity of the subject's participation in the investigation, the details of the investigation, and any other information contained in the informed consent.[3] The subject, LAR, or family member must also be notified that participation in the investigation may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled.[4]

At FDA, a MAPP documents internal agency policies and procedures, as well as federal directives. MAPPs are posted online to provide greater Agency organizational transparency through public access. Because they are internal organizational and operational documents, however, they are not posted for notice and comment, and typically notice of revision is not provided in the Federal Register.

Updates to the MAPP

While the MAPP does not impose any requirements that did not previously exist, it spells out the requirements in greater detail than the previous MAPP and places greater emphasis on efforts to seek informed consent. In addition, it updates the relevant review divisions, which have been reorganized since 2003, and moves responsibility for review back to the Office of New Drugs (OND) review staff, rather than referring all INDs involving an exception from informed consent requirements under section 50.24 to the Office of Scientific Investigations (OSI, formerly the Division of Scientific Investigations).

- **Community consultation:** The revised MAPP provides far more detailed background information, outlining each of the required components of an exception from informed consent for an emergency research IND. In doing so, it places additional emphasis on the need to obtain informed consent, when possible, from the subject or from the subject's LAR, or to provide a family member with an opportunity to object. The former MAPP focused a great deal of attention on the requirement for community consultation to ensure that IND submissions included adequate plans for consultation with and public disclosure to communities where the research would take place. The revised MAPP elaborates on the original definition of "community consultation," to emphasize two-way communication, describing it as "discussion initiated with and by a wide group of community representatives (i.e., two-way communication)," and specifically noting that the views should be elicited so that an IRB can better consider the perspectives of the community in its deliberations.[5] Additionally, when discussing public disclosure, the MAPP provides not just for dissemination of information about the trial and study results afterwards, but also additional disclosures as the IRB determines appropriate.

- **Seeking informed consent:** The revision includes new detail about the lengths to which investigators must go in attempting to obtain informed consent. These requirements are consistent with the regulation but were not included in the original MAPP. In the revised MAPP, where the background discusses the vulnerability of the research population, it mentions not just the inability of the subject to give informed consent or actively refuse, but also the fact that a LAR, who could provide consent, is also not expected to be available within a reasonable amount of time. In each reference to attempts to obtain informed consent from the subject, the MAPP now also includes reference to the inability of investigators to obtain informed consent from a LAR. If obtaining consent from the subject is not feasible and a LAR is not reasonably available, the new MAPP includes a full discussion of the requirement in section 50.24 that an investigator commit to attempt to contact, within the therapeutic window, a patient's family member who is not a LAR, to ask if the family member objects to the patient's participation. Further discussion that was not in the original document focuses on the importance of seeking consent from the subject or the subject's LAR at the earliest possible opportunity, even after enrollment, and, if a LAR is not reasonably available, continuing to look for a family member to provide the chance to object to the subject's continued participation. The MAPP also emphasizes that if the subject's condition later improves, the subject is to be informed about his/her enrollment in the investigation and given the option to discontinue participation at any time.

  This focus on the efforts an investigator must make to seek informed consent may simply result from the revision's focus on the requirements of section 50.24. More broadly, it may also indicate that the Agency is shifting its review emphasis. The compromise permitted by section 50.24 with regard to the Agency's otherwise strict requirement of written informed consent is a tense one, and it would be reasonable for the Agency to ensure as far as possible that every case in which the waiver is used is one in which informed consent could not be obtained. Accordingly, IND sponsors should provide extensive detail in their IND submissions that clearly sets forth the proposed plans for seeking informed consent where possible, attempting to contact a LAR within the proposed therapeutic window (with a strong justification for the proposed therapeutic window), and the measures the sponsor will take to reach out to a family member. The efforts made should also be summarized adequately for continuing review.

- **Clinical hold:** A new section has been added regarding the determination of whether a proposed trial may proceed or should be placed on clinical hold. This section suggests that the decision should be based on "scientific-medical aspects of the trial and the ability to meet the specific requirements of §§ 50.24 and 312.42(b)(5)," but places even stronger emphasis on review team concerns about whether an informed consent document may be "misleading, inaccurate, or incomplete in a way that raises a significant safety or ethical concern for potential trial participants."[6]

- **New checklist:** The revised MAPP includes a detailed checklist for the review of IND submissions requesting an exception from informed consent for emergency research. This checklist includes useful information about the review process, such as the types of consults that might be requested and the time period in which each division must respond. It also lists the criteria a reviewer will use to assess an IND and the steps reviewers will take in seeking additional information. Accordingly, it is a valuable tool for IND sponsors. Sponsors should use the checklist in developing their INDs to ensure that they clearly provide all information that the Agency will need to know. Additionally, the checklist can be used by sponsors to understand where in the process of review their IND may be after submission.

As a consequence of updating the MAPP, FDA has also updated the titles of the divisions and components involved in review of the IND. As the MAPP indicates, primary responsibility for review of an IND requesting an exception from informed consent for emergency research has been moved back to the Office of New Drugs where consults from other divisions will be requested. The office dealing with human subjects protections is now titled the Office of Good Clinical Practice. In addition, the Division of Scientific Investigations is now the Office of Scientific Investigations. Based on the clarification and updates in the new document, it will be easier for sponsors to directly contact the appropriate officials within the Agency.

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King & Spalding will continue to monitor updates to review policy and procedures for INDs requesting an exception to the requirement of informed consent in emergency research under 21 C.F.R. § 50.24. Please let us know if you would like assistance in applying the newly revised MAPP to the development and submission of an IND.

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[1] MAPP § 6030.8 is available online at: http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm082027.pdf
[2] 21 C.F.R. § 50.24(a).
[3] 21 C.F.R. § 50.24(b).
[4] *Id.*
[5] MAPP § 6030.8 at 3-4.
[6] MAPP § 6030.8 at 10.