
POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

INDs: Exception From Informed Consent Requirements for Emergency Research

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Requesting the Exception From Informed Consent for
Emergency Research Under 21 CFR 50.2414

PURPOSE

- This MAPP describes policies and procedures for consistent review and administrative oversight of an investigational new drug application (IND) for emergency research in which the clinical investigation includes a request, pursuant to 21 CFR 50.24, for an exception from the requirement to obtain informed consent from patients.¹
- This MAPP does *not* apply to emergency treatment 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 (see also the definition of emergency use at 21 CFR 56.102(d)) or to an emergency

¹ For important information relevant to adherence to this MAPP, Center for Drug Evaluation and Research staff are encouraged to read the guidance for institutional review boards, clinical investigators, and sponsors *Exception From Informed Consent Requirements for Emergency Research*. This guidance contains frequently asked questions, definitions of regulatory terminology, clinical trial design concerns, and a suggested flow chart for fulfilling the requirements for § 50.24 trials. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

situation that does not allow time for submission of an IND as provided under 21 CFR 312.310(d) (i.e., “emergency procedures” for individual patients).

BACKGROUND

- Trials designed with an exception from informed consent requirements, although uncommon, can raise complex scientific and ethical considerations as well as clinical trial design and conduct challenges. Section 50.24 was developed to make important research possible for patients with a life-threatening condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory) and who, because of their condition, cannot provide informed consent.²
- In rare circumstances, it may be possible to obtain informed consent for emergency research from the patient or the patient’s legally authorized representative (LAR) before entry into the trial. Therefore, although these investigations involve an *exception* from informed consent under § 50.24 that allows the investigation to proceed without consent, the regulations require institutional review boards (IRBs) to review and approve an informed consent document and informed consent procedures that explain how the investigator will attempt to obtain informed consent from the patient or the patient’s LAR, if possible, before the patient is enrolled (§ 50.24(a)(5) and (6)).
- Section 50.24 describes the conditions that must be documented before an exception from informed consent may be approved. These conditions include the following:
 - Aspects of the disease and its treatment
 - Patients must be in a life-threatening situation that necessitates intervention
 - Available treatments are unproven or unsatisfactory
 - Collection of scientific data are necessary to determine the safety and efficacy of the investigational drug
 - Aspects of the informed consent process
 - Patients are unable to give informed consent because of their medical condition

² See § 50.24 for the full list of eligibility criteria.

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- The intervention is time sensitive and must be administered before an LAR can give consent on the patient's behalf
 - Patients cannot be prospectively identified as potential participants
 - Participation in research holds out the prospect of direct benefit to the patients
 - Nonclinical studies have been conducted, and the results of the studies and related evidence support the potential for direct benefit to the patients
 - The risks are reasonable compared to what is known about the patients' medical condition, the risks and benefits of standard therapy (if any), and what is known about the potential risks and benefits of the investigational drug
 - The investigation could not be practicably carried out without the waiver
 - The protocol defines the length of the potential therapeutic window,³ and the principal investigator has committed to attempting to contact the LAR within the therapeutic window, and, if feasible, ask for consent. The clinical investigator must summarize efforts made to contact the patient's LAR and make this information available to the IRB at the time of continuing review.
 - The IRB has approved an informed consent document and informed consent procedures, to use when obtaining informed consent is feasible.
 - 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 and for whom an LAR, who could provide consent, is not available within a reasonable amount of time. This lack of autonomy creates a special need for FDA, sponsors, IRBs, and clinical investigators to work together to ensure that the interests of this vulnerable population are protected. The regulations for emergency research, which describe an exception from the informed consent requirement, contain specific steps to enhance human patient protection in addition to the usual requirements for clinical trials conducted under an IND.
 - The additional protections include at least the following:
 - Community consultation. *Community consultation* has been interpreted by FDA to mean discussion initiated with and by a wide group of community representatives (i.e., two-way communication). It helps ensure

³ The therapeutic window for an investigational drug is the time period after onset of the event, based on available scientific evidence, within which the investigational drug must be used or administered to have its potential clinical effect (diagnostic or therapeutic). See Definitions.

that the communities in which the emergency research will be conducted and from which patients will be drawn are adequately informed about the risks and potential benefits of the research and are given the opportunity to ask questions and express their views before the IRB makes a determination about the research. (See Definitions.)

- Public disclosure of the study and of the trial results. *Public disclosure* has been interpreted by FDA to mean dissemination of information by the sponsor (i.e., one-way communication) to the community, the public, and researchers about emergency research. It occurs before initiation of the clinical trial, after the trial has been completed, and whenever the IRB determines that new disclosures are appropriate. (See Definitions.) Copies of information disclosed to the public under § 50.24 must be submitted to the IND file and to Docket Number 95S-0158, Division of Dockets Management (21 CFR 312.54(a)).
 - Oversight by an independent data monitoring committee (DMC).
 - Commitment by the investigator to attempt to contact, within the therapeutic window, a patient's family member who is not an LAR to ask if the family member objects to the patient's participation in the clinical trial if obtaining informed consent from the patient is not feasible and an LAR is not reasonably available. The clinical investigator must summarize efforts made to contact the patient's family members and make this information available to the IRB at the time of continuing review.
- The *contents*⁴ of both community consultation and public disclosure include information about the clinical trial and its risks and expected benefits, and a summary of the protocol and trial design, among other things. Some *methods that could be used* to conduct community consultation and public disclosure include focus groups, random digit telephone surveys, and radio announcements, among others.
- Each clinical trial protocol that includes an exception from informed consent under § 50.24 must be submitted in a separate IND (21 CFR 312.20(c)); that is, protocols for clinical trials 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 protocol involving this exception, even if an IND for a different protocol involving an exception under § 50.24 for the same drug already exists (§ 50.24(d)).

⁴ For a complete discussion of the contents of the community consultation and public disclosure, see the guidance for institutional review boards, clinical investigators, and sponsors *Exception From Informed Consent Requirements for Emergency Research*.

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- Section 312.20(c) requires that INDs for emergency research conducted under § 50.24 be submitted to and granted written authorization by FDA before the sponsor can proceed. FDA must provide a written determination 30 days after it receives the IND or earlier. Sections 50.25 and 312.23 describe the required contents of such an IND application. Section 312.23(f) requires that the cover sheet (Form FDA 1571) prominently identifies that the investigation is subject to § 50.24.
 - If necessary, FDA may place a proposed or ongoing investigation involving an exception to informed consent under § 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 (§ 312.42(b)(5)).⁵

POLICY

- The Center for Drug Evaluation and Research (CDER) will ensure that applications involving an exception under § 50.24 comply with submission, content, and format requirements under §§ 312.20(c) and 312.23 in addition to the requirements under § 50.24.
- The Office of New Drugs (OND) review staff will be primarily responsible for the review of the exception under § 50.24 and will consult with the Office of Scientific Investigations (OSI). OND review staff will request additional consults from additional CDER offices, the Office of Good Clinical Practice (OGCP), or others as needed.
- In addition to the requirements of § 312.23, CDER will ensure the IND complies with the following:
 - Involves human subjects who are in a life-threatening situation and cannot consent because of their medical condition
 - The collection of valid scientific evidence is necessary to determine the safety and effectiveness of the proposed intervention
 - Appropriate animal and other nonclinical studies have been conducted, and information derived from those studies and related evidence support the potential for the investigational drug to provide a direct benefit to the individual patients (§ 50.24(a)(3)(ii))

⁵ See MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)* and § 312.42, Clinical holds and requests for modification, for more information on clinical hold procedures.

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- The risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of patients, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed investigational drug (§ 50.24(a)(3)(iii))
 - Additional information in the investigational plan is adequate, as required by § 50.24, to address the following points:
 - A justification for why the clinical investigation could not be practicably carried out without the waiver
 - A justification as to why participation in research holds out the prospect of direct benefit to patients
 - A description as to why available treatments are unproven or unsatisfactory
 - A description of why patients likely to be eligible for participation in the clinical investigation cannot be prospectively identified
 - A rationale for selecting the therapeutic window in which the investigational drug is to be used
 - A description of the investigator's commitment to attempting to contact an LAR for each patient within the therapeutic window to ask for consent (§ 50.24(a)(5)) or to contact a family member to provide an opportunity to object to the patient's participation if obtaining informed consent is not feasible and an LAR is not reasonably available (§ 50.24(a)(7)(v))
 - CDER will request formal submission of a copy of the informed consent procedures and informed consent documents for all applications involving an exception under § 50.24 if it has not already submitted to the IND.
 - CDER will also request formal submission of the contents of and plans for community consultation and public disclosure required by §§ 50.24(a)(7)(i) and 50.24(a)(7)(ii), respectively, as other relevant information needed for review of the application under § 312.23(a)(11) if not already submitted to the IND. The IRB has primary responsibility for reviewing the informed consent documents, community consultation materials, and public disclosure for all clinical trial sites under its jurisdiction. However, CDER's subsequent review of IRB-approved materials is particularly important to determine whether a clinical investigation may safely proceed under § 50.24 and part 312.
 - CDER will request formal submission of a list of DMC members and a written DMC charter defining processes and procedures sufficient to address the

requirement in § 50.24(7)(iv) for an independent DMC to oversee the clinical investigation if not already submitted to the IND.

- CDER will review an informed consent exception IND under the provisions of § 50.24 in accordance with the procedures specified below.

RESPONSIBILITIES AND PROCEDURES

CDER OND Regulatory Project Management Staff will:

- Promptly notify the division director and FDA's Senior Bioethicist in OGCP of a § 50.24 submission.
- Request that the sponsor resubmit a separate IND for each emergency research protocol involving an exception from informed consent, if more than one protocol is included in the IND, or if the protocol is submitted as an amendment to an already active IND.
- Determine whether IND submissions that propose exceptions from the informed consent requirements are complete and consistent with regulatory submission requirements.
 - Request submission of the informed consent document(s) and informed consent procedures from the sponsor if not submitted to the IND.
 - Request submission of the contents of community consultation and public disclosure if they were not submitted to the IND. Request confirmation of submission of publicly disclosed materials to the docket if the sponsor did not indicate submission to the docket in the IND.
 - For an original IND under § 50.24, ensure that the sponsor has submitted a copy of the information that was publicly disclosed *before initiation of the trial* to the IND as described in Attachment 1.
 - Request submission of a list of DMC members and written DMC charter defining processes and procedures if they were not submitted to the IND.
 - Verify IRB approval, or if not approved, that the information related to an IRB's determination that it cannot approve a clinical trial because of failure to meet criteria for the exception from informed consent in § 50.24(a) or other relevant ethical concerns has been submitted to the IND, as required by §§ 312.54(b) and 50.24(e).

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- Follow standard procedures to ensure proper tracking of this type of IND in CDER's regulatory data archiving and tracking system.
 - Ensure that the Application Property Type "Exception from Informed Consent" is selected in the electronic archiving and tracking system

 - Prepare and issue an acknowledgment letter that notifies the sponsor in writing of the date the IND was received under § 312.40(b)(2) and reminds the sponsor of the requirement for an IND under § 312.20(c), specific to § 50.24. Use the acknowledgment letter "Acknowledge Informed Consent Exception IND" available in the CDER Standard Templates (CST) repository. This should be issued using standard procedures to ensure proper tracking of this type of IND in CDER's regulatory data archiving and tracking system.
 - The acknowledgment letter should include a reminder of the requirement to submit a copy of the information publicly disclosed *following completion of the trial* to the IND as described in Attachment 1

 - Within 7 calendar days of receipt of a complete set of materials (e.g., request for exception, protocol, informed consent document, informed consent procedures, contents of community consultation and public disclosure, and DMC materials):⁶
 - Consult OSI to review the materials. If other offices (e.g., ethics or biometrics) have been consulted, inform OSI of this.
 - Consult, as needed, FDA's Senior Bioethicist in OGCP to review the materials. If other offices (e.g., biometrics) have been consulted, inform the OGCP of this.
 - Consult other CDER offices (e.g., Office of Biometrics, Office of Medical Policy), as needed.

 - Prepare and issue a letter to the sponsor, **no later than 30 days after receipt of the IND**, to inform it of the review division's decision as to whether the proposed trial may proceed, noting any deficiencies or problems identified. Use the appropriate letter template, either one of the clinical hold letter templates or the "Informed Consent Exception May Proceed" letter available in the CST repository. This should be issued using standard procedures to ensure proper tracking of this type of IND in CDER's regulatory data archiving and tracking system.

⁶ For a complete listing on the contents of the community consultation and public disclosure, see the guidance for institutional review boards, clinical investigators, and sponsors *Exception From Informed Consent Requirements for Emergency Research*.

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- Use section A of Attachment 1 to facilitate oversight of IND submissions requesting exception from informed consent requirements under § 50.24.
 - Notify OSI when annual reports and final reports for INDs submitted under § 50.24 are received.

CDER OND Review Staff will:

- Review IND submissions that propose exceptions from the informed consent requirements to determine if the submission meets each requirement under § 50.24 in addition to the IND regulations described in part 312.
- Evaluate IND submissions for scientific-medical appropriateness, including whether the protocol design will result in collection of useful and necessary data about the safety and effectiveness of the investigational drug being evaluated and whether participation in the research holds out the prospect of direct benefit to the patients. For example:
 - Does information from animal and other nonclinical studies and related evidence support a conclusion that the patients participating in the trial may directly benefit from their participation?
 - Could the data be obtained from an alternate trial approach 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 patients that will be given neither available treatment (if any) nor the investigational drug?
- Discuss informed consent procedures, informed consent document, and community consultation and public disclosure plans and materials with OSI as needed. The review division often has the best expertise to assess whether the description of the risks and benefits of the investigational drug and the trial design are adequately described in these materials.
- Review the DMC materials, including the membership and charter defining the DMC processes and procedures, to ensure that appropriate monitoring provisions have been made.
- Determine if consults with other CDER offices are needed (e.g., Office of Biometrics and Deputy Center Director for Clinical Science on issues related to trial design, and Office of Medical Policy, on an as-needed basis, on policy issues

related to good clinical practice, human subject protection, and trial design). Notify the OND regulatory project manager (RPM) if such a consult is needed.

- Consult FDA's Senior Bioethicist in OGCP if the review staff is not experienced with reviewing trials that include an exception for informed consent or for questions about ethical concerns, including but not limited to the trial and/or informed consent, community consultation and/or public disclosure plans and materials, or receipt from the sponsor of a report of an IRB's determination that the IRB cannot approve the emergency research because of failure to meet the criteria in the exception under § 50.24(a) or because of other relevant ethical concerns.
- Determine whether the proposed trial may proceed or should be placed on clinical hold.
 - The review division should make the decision of whether to place a clinical trial involving exception from the informed consent requirements for emergency research on clinical hold after evaluating the scientific-medical aspects of a trial and the ability to meet the specific requirements of §§ 50.24 and 312.42(b)(5).
 - In some situations, the review division, taking into account the input of OSI and others, may find an informed consent document to be misleading, inaccurate, or incomplete in a way that raises a significant safety or ethical concern for potential trial patients, and require that specific 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 received⁷ or work with the sponsor to incorporate the revisions into the consent document before initiation of the trial (i.e., before the end of the initial 30-day review).
- Use section B of Attachment 1 to facilitate oversight of IND submissions requesting exception from informed consent requirements under § 50.24.

CDER OSI Staff will:

- Review the protocol, informed consent procedures and informed consent document, DMC materials, and the contents of community consultation and public disclosure to ensure that relevant requirements of § 50.24 are met and that they conform to FDA guidance.
- Complete a written review indicating agreement or nonagreement with: (1) the informed consent procedures and document for appropriateness; and (2) the

⁷ See MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)* and § 312.42, Clinical holds and requests for modification, for more information on clinical hold procedures.

contents of community consultation and public disclosure. The review should indicate whether these documents and procedures conform to FDA regulations and guidance.

- Archive the written review within 10 business days of receipt of the IND consult request in CDER's regulatory data archiving and tracking system.
- Review the annual and final reports to determine the need for an IRB inspection.

ETHICS REVIEW

- The Senior Bioethicist in the OGCP tracks INDs for emergency research in which the clinical investigation includes a request for an exception from the requirement to obtain informed consent from patients
- If the review division requests a consult, an ethics review involves:
 - Review of the IND submission materials to evaluate the ethical acceptability of the submission and conformance with applicable regulations (e.g., § 50.24; parts 50, 56, and 312) and FDA policies, and to address any questions posed by the consulting review division or that are identified during the ethics review
 - Completing a written review indicating agreement or nonagreement with the ethical acceptability of the submission and its conformance with applicable regulations, and identification of other concerns
 - Archiving the written review within 10 business days of receipt of the IND consult request in CDER's regulatory data archiving and tracking system

REFERENCES

Rules and Regulations

- 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
- Final rule “Protection of Human Subjects; Informed Consent” (61 FR 51498, October 2, 1996)

Guidances

- Guidance for institutional review boards, clinical investigators, and sponsors
Exception From Informed Consent Requirements for Emergency Research
(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)

MAPPs⁸

- MAPP 4151.1 Rev. 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*
- MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*
- MAPP 6030.2 Rev. 1 *INDs: Review of Informed Consent Documents*

Other

- A Guide to Informed Consent — Information Sheet Guidance for Institutional Review Boards and Clinical Investigators
(<http://www.fda.gov/regulatoryinformation/guidances/ucm126431.htm>)

⁸ MAPPs are available on the MAPP Web page at
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

DEFINITIONS⁹

Community consultation. Community consultation means providing the sponsor the opportunity for discussions with, and soliciting opinions from, the community or communities in which the clinical trial will take place and from which the patients will be drawn, about the clinical trial.

Legally authorized representative (LAR). An individual or judicial or other body authorized under applicable State or local law to provide informed consent on behalf of a prospective patient to the patient's participation in the research (21 CFR 50.3(m)). IRBs and clinical investigators should familiarize themselves with applicable local statutes and regulations pertaining to the definition of a legally authorized representative.

Public disclosure. Dissemination of information by the sponsor about the emergency research sufficient to allow a reasonable assumption that the communities are aware of the plans for the investigation, its risks and expected benefits, and the fact that the clinical trial will be conducted without obtaining informed consent for most or even all patients. Public disclosure also includes dissemination of information about the results of the trial after the investigation is completed so that the communities and scientific researchers are aware of the trial results.

Therapeutic window. The therapeutic window is: (1) the time period, based on available scientific evidence, during which administration of the investigational drug might reasonably produce a demonstrable clinical effect; or (2) for investigations of in vitro diagnostic devices that meet the criteria for emergency research, the therapeutic window is the time period, based on available scientific evidence, during which diagnosis must occur to allow administration of appropriate therapy.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
02/04/2003	n/a	Initial issuance
11/17/14	Rev. 1	Responsibility and procedural update for CDER staff and addition of checklist for RPMs and reviewers.

⁹ As defined in the guidance for institutional review boards, clinical investigators, and sponsors *Exception From Informed Consent Requirements for Emergency Research*.

ATTACHMENT 1¹⁰Checklist for IND Submissions Requesting the Exception From Informed Consent for
Emergency Research Under 21 CFR 50.24**A. Regulatory Project Manager****1. Consults, Notifications, and Regulatory Reviews (each item should be answered as “Yes,” “No,” or “N/A”)**

- _____ Division director(s) has been notified of a § 50.24 protocol submission
- _____ OSI has been consulted
_____ Consult review received
- _____ Office of Biometrics or Deputy Center Director for Clinical Science has been consulted, if needed
_____ Consult review received
- _____ FDA’s Senior Bioethicist in the OGCP has been notified of the § 50.24 submission
- _____ FDA’s Senior Bioethicist in the OGCP has been consulted, if needed to provide assistance, expertise, or input on ethical issues
_____ Consult review received
- _____ Other CDER offices (e.g., Office of Medical Policy, Office of Biostatistics) have been consulted, if needed
_____ Office(s) consulted _____ Consult review(s) received
- _____ Progress toward completion of review is being monitored, specifically addressing each requirement under § 50.24 with recommendations as needed

2. Adequacy of Protocol Submission and Materials (classify each item as: “OK” if adequate, “INC” if incomplete (i.e., process in progress — to be completed later), or “NA” if not applicable)

- _____ Verify submission of a separate IND for clinical trial protocols involving an exception to the informed consent requirements under § 50.24 that clearly identifies such protocols as protocols that may include patients who are unable to consent (*submission as separate IND is required even if an IND for the same drug already exists; amendments under § 312.30 are not acceptable*)

¹⁰ This attachment also may be useful for OSI staff and other FDA components consulting on IND submissions under § 50.24.

_____ Verify submission of a complete set of materials (e.g., request for exception, protocol, informed consent document, informed consent procedures, contents of community consultation and public disclosure)

If materials specifically required under § 50.24 are incomplete:

_____ Notify the sponsor that information concerning the public disclosures required by § 50.24(a)(7)(ii) must be promptly submitted to the IND

_____ Verify that information concerning public disclosures required by § 50.24(a)(7)(ii) has been submitted to the IND

_____ Verify that the information related to an IRB's determination that it cannot approve a clinical trial because of failure to meet criteria for the exception from informed consent in § 50.24(a) or other relevant ethical concerns has been submitted to the IND, as required by § 312.54(b)

After the trial has been completed:

_____ After public disclosure plans and materials following completion of the clinical trial are submitted, verify that the information is complete as described in the initial IND submission

If OND becomes aware that the public disclosure plans and materials were not submitted:

_____ Notify the sponsor that information concerning the public disclosures required by § 50.24(a)(7)(iii) must be promptly submitted to the IND

_____ Verify that information concerning public disclosures required by § 50.24(a)(7)(iii) has been submitted to the IND

_____ Notify the sponsor as well as the OSI accordingly when the required information concerning the public disclosures following completion of the clinical trial (as noted above) has not been submitted

B. Reviewer

Note: All reviews of clinical trial protocols proposing waiver of the informed consent requirements should address specifically each of the following summarized components of § 50.24 (i.e., for each item on the checklist below, the review should include a brief summary of how the application does or does not address each IRB finding as required by § 50.24).

_____ Available treatments unproven or unsatisfactory

_____ Valid scientific evidence is necessary to determine safety and effectiveness of the investigational drug to be studied

_____ Valid scientific evidence regarding safety and effectiveness of the investigational drug will be obtained by the proposed trial, as designed

Obtaining Informed Consent not Feasible because:

_____ Patients unable to give informed consent as a result of medical condition;

_____ Investigational drug must be administered before consent from the patients' LARs is feasible; **and**

_____ Eligible patients cannot be identified prospectively.

Prospect of Direct Benefit to patients because:

_____ Patients face a life-threatening situation that necessitates intervention;

_____ Information from animal or other nonclinical studies and related evidence support potential for direct benefit to individual patients; **and**

_____ Risks reasonable in relation to patients' medical condition, risks-benefits of standard therapy, and risks-benefits of the investigational drug(s).

Clinical Trial and Consent Requirements

_____ Trial could not be practicably carried out without waiver of informed consent;

_____ Protocol defines the length of the potential therapeutic window based on scientific evidence;

_____ Investigator has committed to attempting to contact an LAR for each patient within that time window if feasible to ask for consent; **and**

_____ Investigator has committed to summarizing efforts to contact LARs, and providing summary of such efforts to the IRB at the time of continuing review.

Additional Protections of Patients' Rights and Welfare, including (before starting):

_____ Specified contents of **community consultation**

_____ Specified contents of **public disclosure**

_____ DMC oversight is adequate, as evidenced by experienced DMC membership and written DMC charter defining processes and procedures

Additional Consent and Information Requirements

_____ If informed consent is not feasible and the LAR is unavailable, the protocol specifies commitment to attempt to contact (within the therapeutic window) the patient's family member who is not an LAR, and ask whether he or she objects to the patient's participation (the investigator must specify that he or she will summarize efforts to contact family members and make this information available to the IRB at the time of the continuing review); the IRB is responsible for ensuring that procedures are in place to address this requirement

_____ The clinical trial protocol specifies that each patient will be informed at the earliest opportunity of the patient's inclusion in the trial, details of the trial, and other information in the informed consent document (if the patient remains incapacitated, such information must be given to the LAR, or if the LAR is not reasonably available, to a family member); the IRB is responsible for ensuring that procedures are in place to address this requirement

_____ The clinical trial protocol specifies procedures to inform the patient, or if the patient remains incapacitated, the LAR, or if unavailable, a family member, that he or she may discontinue the patient's participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

_____ The clinical trial protocol specifies that if the LAR or a family member is told about the trial and the patient's condition improves, the patient will also be informed as soon as feasible

_____ The clinical trial protocol specifies that if the patient entered into the trial and dies before the LAR or family member can be contacted, information about the trial will be provided to the patient's LAR or family member, if feasible