

SOP#: RPS-17

**Expanded Access IND/Protocol Submissions to the
FDA and IRB**

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POLICY

Expanded access refers to the use of an **investigational drug (and biological drug)** product when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. The regulations are intended to facilitate access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives.

21 CFR 312 (Subpart I) describes three distinct categories of expanded access: Individual Patient (including for Emergency Use); Intermediate-Size Patient Populations; and Treatment IND or Treatment Protocol.

For each category of expanded access, two types of submissions can be made to the FDA: 1) a new IND; or 2) an expanded access protocol submitted as a protocol amendment to an existing IND.

An investigator treating a patient under expanded access is responsible for obtaining full board IRB review before treatment can begin, except in cases of individual patient, emergency expanded access use when there is not enough time to secure prospective IRB review. In such cases the IRB must be notified of the emergency expanded access use no later than 5 working days after treatment. A physician submitting a new individual patient expanded access IND may request a waiver regarding full IRB review; such a waiver is appropriate when the physician obtains concurrence by the IRB chairperson before treatment use begins.

PURPOSE

To describe the process for submission of an individual expanded access IND/protocol to the FDA and the NIH IRB. The CCR Office of Regulatory Affairs will be responsible for coordinating the submissions to both regulatory bodies.

RESOURCES

- 21 CFR 312 Subpart I:
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9>
- FDA guidance Expanded Access to Drugs for Treatment Use 2017:
<https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>
- Individual Expanded Access Applications: Form 3926:
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf>

PROCEDURES

Step 1: FDA requirements

Type of Expanded Access	FDA review	IRB review
Individual Patient Emergency IND or Individual Patient Emergency Protocol (submitted as an amendment to existing IND)	FDA may authorize use via phone (or other rapid means of communication) in advance of official/written submission. Written submission required within 15 working days of FDA authorization.	Not required prior to treatment. IRB notification required within 5 working days of initiation of treatment. A physician submitting a new individual patient expanded access IND may request a waiver regarding full IRB review; such a waiver is appropriate when the physician obtains concurrence by the IRB chairperson before treatment use begins.
Individual Patient Protocol (submitted to existing IND)	Written submission received by the FDA before treatment can begin.	Full board review required. A physician submitting a new individual patient (under expanded access) may request a waiver regarding full IRB review; such a waiver is appropriate when the physician obtains concurrence by the IRB chairperson before treatment use begins.

Type of Expanded Access	FDA review	IRB review
Individual Patient IND	30-day review of written submission.	Full board review required. A physician submitting a new individual patient expanded access IND may request a waiver regarding full IRB review; such a waiver is appropriate when the physician obtains concurrence by the IRB chairperson before treatment use begins.
Intermediate-size Population IND	30-day review of written submission.	Full board review required.
Intermediate-size Population Protocol (submitted to existing IND)	Written submission received by the FDA before treatment can begin.	Full board review required.
Treatment IND/ Treatment Protocol	30-day review of written submission.	Full board review required.

For all types

- Human subject protections apply to all Expanded Access Protocols (EAPs)
 - Part 50, Protection of Human Subjects (informed consent)
 - Part 56, Institutional Review Board
 - Part 312, including Clinical Holds based on safety and reporting requirements (i.e. adverse event reports, final/annual reports)
- The treating physician is responsible for adverse event and outcome reporting to the local IRB, and to the Sponsor (and to the FDA if Sponsor-Investigator IND)
- Manufacturer must be willing to provide product
- Sponsor must be willing to monitor use of product and report to the FDA
- The appropriate technology transfer agreement must be in place prior to use of the product, if the manufacturer is not NCI
- The treating physician must provide:
 - The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options.

- The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition.
- The method of administration of the drug, dose, and duration of therapy.
- The Sponsor must provide:
 - A description of the facility where the drug will be manufactured.
 - Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug.
 - Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated).
 - A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

Requirements for individual patient EAPs, including emergency use (21 CFR 312.310)

- The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition
- Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy
- If requesting emergency use, the following criteria must be met:
 - The patient has a serious or immediately life-threatening disease or condition.
 - There are no comparable or satisfactory alternative treatment options to treat the patient's condition.
 - The potential benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated.
 - The patient's condition requires immediate intervention before review at a convened meeting of the IRB is possible to avoid major irreversible morbidity or death.

Requirements for Intermediate Size Population (21 CFR 312.315)

- Intended for patient populations smaller than intended for Treatment IND (generally up to 100 patients)
- Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population
- Explanation of why drug cannot be developed or why patients cannot be enrolled in a clinical trial:
 - Being developed (e.g. patients not eligible or trial site not accessible)
 - Not being developed (e.g. rare disease, cannot recruit for a trial)

- Approved (e.g. drug withdrawn, drug shortage situation)
- REMS (Risk Evaluation and Mediation Strategy) restricts distribution
- There is preliminary clinical evidence of effectiveness of the drug in the anticipated patient population.

Requirements for Treatment IND or Protocol (21CFR 312.320)

- The drug is being investigated in clinical trials designed to support marketing approval for the expanded access use, or all clinical trials have been completed
- Company/Sponsor is actively pursuing marketing approval of the drug for the expanded access use
- If the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use.

Step 2: Prepare a request for Individual Patient Expanded Access

- Obtain assurance that the manufacturer is willing to provide sufficient drug supply.
- If CTEP is the sponsor, contact the Regulatory Affairs Branch to obtain approval for use of the agent, not the FDA. For more information regarding the CTEP process, see: http://ctep.cancer.gov/branches/pmb/non_protocol_access.htm
- If the Center for Cancer Research is the sponsor of an existing IND for the drug, the CCR may satisfy the submission requirements by amending its IND to include a protocol for individual expanded access.
- A licensed physician may satisfy the submission requirements by obtaining from a non-CCR sponsor, a right of reference for information to support the expanded access request (right of reference) and/or by providing other required information on the Form FDA 3926.

Step 3: Develop a submission package for the FDA

Include the following:

- A memo which states this is a “Request for Individual Patient Expanded Access Use” (specifying if it is an emergency use) at the top of the correspondence.
- Brief Clinical History of the patient including:
 - diagnosis
 - disease status (including lab values if available)
 - prior therapy
 - response to prior therapy
 - rationale for requesting the proposed treatment, including a list of available therapeutic options and why use of the investigational product is preferable to use of available therapeutic options

- Proposed Treatment Plan including:
 - dose
 - route
 - planned duration
 - monitoring procedures to include a description of how the PI will monitor the patient for adverse events and a monitoring plan if the use of the agent will be for an extended duration
 - modifications (e.g. dose reduction or treatment delay) for toxicity
 - Reference published protocols or journal articles as appropriate
- A Letter of Authorization (LOA) referencing the appropriate IND or Master File for the drug. If such an application does not exist, it may be necessary to provide chemistry, manufacturing, controls, preclinical and clinical study information supporting use of the drug.
- Statement that informed consent and IRB approval will be obtained prior to initiating drug treatment or a request for waiver of IRB review.
- Investigator Qualification Statement that specifies the training, experience, and licensure of the treating physician. The first two pages of a Curriculum Vitae (C.V.) typically contain this information and are usually sufficient if submitting the request using a Form FDA 3926. Include Form FDA 1572 if submitting a new IND or new protocol to an existing IND using a Form FDA 1571

Step 4: Submit all documents to the CCR IND manager for submission to the FDA

Emergency Procedures

If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize treatment by telephone (or other rapid communication).

- If contacted by phone or email to request individual patient, emergency, expanded access use the FDA usually responds within 1 day. The Sponsor must agree to submit written documentation to the FDA within 15 working days after authorization is granted.
- Once the IND number is provided by the FDA, proceed with submitting the request to the NIH IRB via iRIS using the “Emergency Use IND form”.

Non-emergency Procedures

- The FDA will have 30 days to complete their review of a new Expanded Access IND.
- If an individual patient expanded access protocol is submitted to an existing IND, there is no FDA review period, however the protocol must receive IRB approval consistent with 21 CFR part 56, before treatment can begin.

Step 5: Submitting a request to the IRB for an emergency use IND

No DEC clearance is required for an individual patient, emergency use expanded access IND.

- Revise or create an informed consent document
 - Use term “experimental regimen” where appropriate, revise title and protocol number
 - Remove watermark
 - Revise to include information only pertinent to the patient including treatment regimen and follow up
- Initiate the submission in iRIS
 - In iRIS, Click on New Study from the Menu Bar
 - Complete the Study Application
 - Do not submit the Emergency Use IND form within an existing study in iRIS. Expanded Access protocols are considered independent protocols.
 - Complete the submission form for the Emergency Use IND (do not use the Initial Review submission form in this case)
 - Upload consent in iRIS
 - Include documentation of FDA review (a copy of the email or a memo detailing the teleconference between the NCI and FDA).
 - Submit and route for PI and Clinical Director signatures. Route to any additional NIH employee KSP that were included in the study application.
 - After all required signatures are obtained, the final informed consent is uploaded in iRIS by the IRB administrative office.
 - The individual Emergency Use protocol is not processed by OPS, and the consent is not posted on the web

Step 6: After the patient is treated

- Five days following patient treatment a follow up report should be submitted to the IRB using the Emergency Use IND submission form.
- Add a new form, select that this is a “follow up” report, and complete the required information.
- Route this form to both the PI and Clinical Director for signatures in iRIS.
- Individual Emergency Use expanded access protocols should be closed in iRIS once the patient has completed treatment. Use the study closure submission if the treatment has concluded or complete a continuing review submission form each year if the individual IND needs to stay open/the patient is continuing treatment.
- Data from this patient may not be combined (included) with data from patients treated on a similar protocol in a final study report or publication.
- When the patient has completed treatment, a copy of the follow up report should be provided to the Sponsor; a final report must be submitted to the IND along with the request for the IND to be withdrawn.