Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products

Guidance for IRBs and Clinical Investigators

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Dat Doan, 240-402-8926.

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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September 2023
Good Clinical Practice (GCP)

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10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
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Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
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Contains Nonbinding Recommendations

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Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products Guidance for IRBs and Clinical Investigators[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to institutional review boards (IRBs) and clinical investigators regarding the key factors and procedures IRBs should consider when reviewing individual patient expanded access submissions, including for reviews conducted by a single member of the IRB, to fulfill its obligations under 21 CFR part 56. Although FDA has issued guidance on expanded access requests, including expanded access for individual patients,[2] the Agency is aware that IRBs seek further clarity on this topic.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Office of Clinical Policy (OCLiP), and the Oncology Center of Excellence (OCE) at the Food and Drug Administration.

[2] See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* (November 2022). When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (October 2017) and the information sheet guidance for sponsors, clinical investigators, and IRBs *Waiver of IRB Requirements for Drug and Biological Product Studies* (October 2017). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. BACKGROUND

Expanded access refers to the use of an investigational drug[3] 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.[4] This pathway, sometimes called "compassionate use," allows a patient with a serious or immediately life-threatening disease or condition[5] to gain access to an investigational drug or biological product when there is no comparable or satisfactory alternative therapy; the potential patient benefit justifies the potential risks to the patient, and those risks are not unreasonable in the context of the disease or condition to be treated; and the requested use will not interfere with clinical investigations that could support marketing approval.[6] For an investigational drug or biological product to be provided through the expanded access pathway, the sponsor of the investigational drug or biological product must agree to provide such access. Although the drug requested under individual patient expanded access is investigational, use of that drug through individual patient expanded access is for the primary purpose of diagnosing, monitoring, or treating a patient's disease or condition, rather than generating scientific data intended to characterize the safety and effectiveness of a drug.[7]

Under FDA regulations, there are three categories of expanded access submissions: individual (also known as single) patient, including for emergency use; intermediate-size for intermediate-size patient populations; and "treatment" for larger populations.[8] This guidance only applies to IRB review of individual patient expanded access submissions as outlined in 21 CFR 312.310.[9]

This guidance does not address IRB review of intermediate-size and "treatment" expanded access submissions, as outlined in 21 CFR 312.315 and 312.320, respectively.

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[3] In this guidance, the terms *investigational new drug*, *investigational drug*, *drug*, and *drug product* refer to human drugs, including biological products, regulated by CDER and CBER.

[4] See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers.*

[5] For the purpose of expanded access to investigational drugs for treatment use, *immediately life-threatening disease or condition* means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. *Serious disease or condition* means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one (21 CFR 312.300(b)).

[6] See 21 CFR 312.300 and 312.305.

[7] See 21 CFR 312.300. See also the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers*.

[8] See 21 CFR 312.310, 312.315, and 312.320.

[9] See 21 CFR 312.310.

An individual patient expanded access request can be submitted to FDA by a licensed physician as a new investigational new drug application (IND) or by a sponsor of an existing IND as a protocol amendment, either on an emergency[10] or non-emergency use basis.[11] A request for emergency individual patient expanded access does not require prior IRB review, but the IRB must be notified within 5 working days of treatment initiation. Generally, once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would require prior IRB review and approval. An institution or physician that expects subsequent use of the investigational drug should request review and approval by the appropriate IRB after the initial emergency use. However, when prior IRB review and approval is not feasible for a subsequent expanded access emergency use at a particular institution, FDA does not intend to deny the subsequent request for emergency use based on lack of time to obtain prospective IRB review, provided that use will be reported to the IRB within 5 working days of initiation of treatment.[12] For non-emergency expanded access requests for individual patients, prior IRB review and approval is required before treatment begins.[13]

A licensed physician who submits a non-emergency individual patient expanded access request may request from FDA a waiver[14] of the requirement for full IRB review.[15] Upon request, FDA intends to allow for waivers of the requirement for full IRB review and approval for individual patient expanded access requests when the physician obtains concurrence from the IRB chairperson or another designated IRB member before treatment begins.[16] A waiver of the requirement for full IRB review would also extend to any changes or amendments to the original treatment plan or for continuing review of the individual expanded access request.

IRB review of an expanded access submission for an individual patient, including review by a designated single member of the IRB under a waiver, should focus on the key factors needed to assess the risks and benefits of treatment for the particular patient involved. As discussed above, FDA is aware that IRBs are seeking clarity regarding the key factors and procedures they should

[10] FDA considers an emergency situation to be, for example, a situation that requires a patient to be treated before a written submission to the IRB can be made and in which the treatment is expected to have a rapid effect in resolving an acute clinical emergency.

[11] See 21 CFR 312.310

[12] See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* and 21 CFR 56.104(c).

[13] See 21 CFR 312.305(c)(4) and 56.103.

[14] See 21 CFR 56.105.

[15] See 21 CFR 56.108(c).

[16] FDA intends to consider a completed Form FDA 3926 with the box in Field 10.b checked and the form signed by the physician to be a request for a waiver. Form FDA 3926, which is a streamlined alternative to Form FDA 1571, was created specifically for physician-submitted individual patient expanded access INDs, including those for emergency use. A physician submitting an individual patient expanded access IND using Form FDA 1571 may include a separate waiver request with the application. See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers*.

consider when reviewing individual patient expanded access requests, including IRB reviews conducted by single members, to fulfill their obligations under 21 CFR part 56. Below, FDA provides recommendations to IRBs on those key factors and procedures to consider.

III. RECOMMENDATIONS ON IRB PROCEDURES AND FACTORS TO CONSIDER FOR INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS

The recommendations in this section are intended to assist IRBs in complying with the requirements under 21 CFR part 56 when reviewing individual patient expanded access requests, including establishing procedures for such requests and factors to consider when assessing the risks and benefits of treatment with the investigational drug for the particular patient involved.

FDA recommends that IRBs:

- Consider establishing procedures for a single IRB member (an IRB chairperson or other designated IRB member) to review a non-emergency individual patient expanded access submission if the physician requests a waiver[17] of the requirements for review by the full IRB.[18] These procedures should reflect the information that the IRB deems relevant for a single IRB member review and should include procedures designed to ensure that the member documents the decision to concur or not concur with the treatment.

- Focus the review of an individual patient expanded access submission on assessing the risks and benefits for the patient involved. The information reviewed by the IRB must be adequate to assess whether risks to the patient have been minimized and that such risks are reasonable in relation to anticipated benefits.[19] FDA regulations under 21 CFR 56.111 outline the criteria for IRB approval of research. In the context of an individual patient expanded access submission, FDA does not expect that a protocol will be necessary to provide the IRB with sufficient information to determine whether those criteria are satisfied.[20] A thorough patient history and treatment plan, included in the Form FDA 3926 or in a separate document, can be sufficient to provide the information necessary for an IRB assessment. Such information should include:

    - The proposed daily dose, route, and frequency of administration of planned treatment; duration of planned treatment; criteria for discontinuation of treatment; and planned dose modifications for adverse events

[17] See 21 CFR 56.105.

[18] See 21 CFR 56.108(c).

[19] See 21 CFR 56.111(a)(1) and (a)(2).

[20] For individual expanded access protocol amendments submitted by sponsors to their existing INDs, the IRB is likely to receive a protocol for review.

- The planned monitoring for adverse events, response to treatment, and changes in clinical status, as well as proposed modifications to the treatment plan to mitigate risks to the patient if appropriate

- The key details of the patient's history, including diagnosis and summary of prior therapy (including response to such therapy); the reason for request, including an explanation of why the patient lacks other therapeutic options; and information regarding a patient's relevant clinical characteristics (such as comorbid conditions and concomitant medications) that is necessary to assess the potential for increased risks of the drug

- A summary of known risks of the drug

The following are also important components of IRB review of an expanded access submission for an individual patient:

- Assess the qualifications of the physician submitting the individual patient expanded access request.[21]

- When the request is for a pediatric patient, confirm that adequate provisions are included for soliciting age-appropriate assent from children and permission from a parent or guardian, as required under 21 CFR 50.55.

- Confirm that the informed consent document contains the information required under 21 CFR 50.25. As described above, the primary purpose of expanded access is to use the drug to diagnose, monitor, or treat a patient's disease or condition rather than to generate scientific information intended to characterize the safety and effectiveness of a drug. 21 CFR 50.25(a)(1) requires that the informed consent include a statement that the use of the product "involves research." Given that the drug used under expanded access is investigational, FDA generally considers a statement in the informed consent document indicating that although the primary use of the drug is for treatment, the drug is investigational, and FDA has not determined that the drug is safe or effective for use in treating the patient's disease or condition to satisfy this requirement.

[21] See 21 CFR 56.107(a) and 56.111 and the guidance for IRBs, clinical investigators, and sponsors *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed* (August 2013).