Expanded Access to Investigational Drugs for Treatment Use Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Clinical Policy (OCLiP)
Oncology Center of Excellence (OCE)

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Contains Nonbinding Recommendations

Expanded Access to Investigational Drugs for Treatment Use Questions and Answers Guidance for Industry[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 information for industry, researchers, physicians, institutional review boards (IRBs), and patients about the implementation of FDA's regulations on expanded access to investigational drugs[2] for treatment use under an investigational new drug application (IND) (21 CFR part 312, subpart I), which went into effect on October 13, 2009.[3] FDA received numerous questions concerning implementation of the regulatory requirements for expanded access. As a result, FDA issued the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* (June 2016, updated October 2017) (the 2017 guidance), providing recommendations in a question-and-answer format, addressing the most frequently asked questions. Since 2017, FDA has received additional questions concerning implementation of the regulatory and statutory requirements of expanded access to investigational drugs, including those added by the 21st Century Cures Act (Cures Act)[4] and the FDA Reauthorization Act of 2017 (FDARA).[5]

[1] This guidance has been prepared by the Office of Medical Policy in 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) and in consultation with the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

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

[3] *Federal Register* of August 13, 2009 (74 FR 40900).

[4] 21st Century Cures Act (Cures Act), Public Law 114-255; 130 STAT.1033, December 13, 2016, Sec. 3032.

[5] See the FDA Reauthorization Act of 2017 (FDARA), Public Law 115-52; 131 STAT.1005, August 18, 2017, Sec. 610.

In a separate guidance,[6] FDA provides answers to questions concerning the implementation of the regulation on charging for investigational drugs under an IND (21 CFR 312.8).[7] Also, in a separate guidance, FDA describes Form FDA 3926 (Individual Patient Expanded Access—Investigational New Drug Application (IND)) and the process for submitting expanded access requests for individual patient INDs.[8]

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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Expanded access refers to the use of an investigational drug 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. FDA has a long history of facilitating expanded access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions[9] who lack satisfactory therapeutic alternatives. Still, a patient cannot receive an investigational drug through the expanded access pathway unless the sponsor[10] of the investigational drug agrees to provide such access.

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[6] See the guidance for industry *Charging for Investigational Drugs Under an IND: Questions and Answers* (February 2024). 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.

[7] See also the *Federal Register* of August 13, 2009 (74 FR 40872).

[8] See the guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (June 2016, updated October 2017).

[9] 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)).

[10] Sponsor means a person (individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization) who takes responsibility for and initiates a clinical investigation (21 CFR 312.3(b)). The sponsor of an investigational drug (existing IND) typically is the pharmaceutical company or manufacturer of the drug.

FDA revised its IND regulations in 2009[11] by removing the existing regulations on treatment use and creating subpart I of part 312 to consolidate and expand the various provisions regarding expanded access to treatment use of investigational drugs.

Under FDA's current regulations, there are three categories of expanded access:

- Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol)[12,13] (21 CFR 312.315)
- Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations) (21 CFR 312.320)

The regulations describe criteria that must be met to authorize expanded access use, requirements for expanded access submissions, and safeguards that are intended to protect patients and preserve the ability to develop meaningful data about the safety and effectiveness of the drug through clinical trials or drug development. The regulations were also intended to facilitate the availability, when appropriate, of investigational new drugs for treatment use while protecting patient safety and avoiding interference with the development of investigational drugs for marketing under approved applications.

The Cures Act added section 561A to the Federal Food, Drug, and Cosmetic Act (FD&C Act) to include new requirements regarding expanded access. Under section 561A of the FD&C Act, the manufacturer or distributor of one or more investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions is required to make its policy for evaluating and responding to expanded access requests (expanded access policy) public and readily available, such as by posting the policy on a publicly available website.[14] The manufacturer or distributor is required to include their contact information, procedures for submission of expanded access requests, general criteria for evaluation and response, the anticipated time frame for acknowledgement of such requests, and a hyperlink or other reference

[11] *Federal Register* of August 13, 2009 (74 FR 40900).

[12] A protocol is submitted as an amendment to an existing IND by the sponsor of the existing IND. See 21 CFR 312.305(b)(1).

[13] For information on the types of regulatory submissions that can be used to obtain expanded access, including treatment INDs or treatment protocols, see Q6 in this guidance.

[14] 21 U.S.C. 360bbb-0(b).

to the record in ClinicalTrials.gov[15] that contains information about availability of the drug under expanded access.[16]

FDARA amended the FD&C Act to require that the expanded access policy for an investigational drug be posted by the earlier of (1) the first initiation of a phase 2 or phase 3 study with respect to such investigational drug or (2) within 15 days after the drug receives a fast track, breakthrough, or regenerative advanced therapy designation.[17] However, the posting of the expanded access policy does not guarantee access to the investigational drug under expanded access.[18] When a sponsor provides expanded access to its drug, it does so voluntarily. FDA cannot compel a sponsor to provide expanded access to its drug.

FDA expects that the public availability of this guidance will increase awareness and knowledge of the availability of expanded access and the procedures for obtaining investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack satisfactory therapeutic alternatives.

III. QUESTIONS AND ANSWERS

A. Expanded Access for Treatment Use

Q1. What is expanded access?

The terms expanded access, access, and treatment use are used interchangeably to refer to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The terms *compassionate use* and *preapproval access* are also occasionally used in the context of the use of an investigational drug to treat a patient. Although the terms *compassionate use* and *preapproval access* have been used informally in the United States and are also used outside the United States, they are not defined or described in FDA regulations. This has led to some confusion or lack of clarity about the meaning of the terms (e.g., whether they refer to all expanded access or to a type of expanded access, such as individual patient expanded access). For this reason, the terms *compassionate use* and *preapproval access* will not be used in this document.

The main distinction between expanded access and the use of an investigational drug in the usual studies covered under an IND is that expanded access uses are primarily to diagnose, monitor, or treat a patient's disease or condition rather than to obtain information about the safety or

[15] ClinicalTrials.gov is a website and online database of clinical research studies and information about their results. It is maintained by the National Library of Medicine. This data bank is a web-based resource that provides the public with easy access to information on certain publicly and privately supported clinical studies on a wide range of diseases and conditions. See https://clinicaltrials.gov.

[16] 21 U.S.C. 360bbb-0(c).

[17] 21 U.S.C. 360bbb-0(f).

[18] 21 U.S.C. 360bbb-0(d).

effectiveness of a drug. Expanded access may also refer to (1) use in situations when a drug has been withdrawn for safety reasons but there exists a limited population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes for patients who cannot obtain the drug under the REMS; or (3) use for other reasons.

Q2. Are there safeguards in place for expanded access use of an unapproved drug?

Yes, there are multiple safeguards in place. Sponsors, investigators, and sponsor-investigators must comply with the responsibilities set forth in 21 CFR part 312, subpart D, to the extent they are applicable to the expanded access use (§ 312.305(c)).[19] For all expanded access INDs, investigators are responsible for reporting adverse events to the sponsor, ensuring that the informed consent requirements in part 50 (21 CFR part 50) are met and ensuring that an IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 (21 CFR part 56) (see Q9 for additional information related to IRB review requirements for different categories of expanded access). Investigators and sponsor-investigators are also responsible for maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62 (see § 312.305(c)(4)). For all expanded access INDs, sponsors are responsible[20] for the following:

- Complying with IND safety reporting requirements under § 312.32
- Submitting to FDA annual reports (when the IND or protocol continues for 1 year or longer) under § 312.33
- Ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use
- Providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug
- Maintaining an active IND for the expanded access use until treatment has concluded and safety monitoring is complete
- Maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57

[19] A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use is considered an investigator (§ 312.305(c)(1)). An individual or entity that submits an expanded access IND or protocol under 21 CFR part 312, subpart I, is considered a sponsor (§ 312.305(c)(2)). A licensed physician who submits an expanded access IND or protocol and under whose immediate direction an investigational drug is administered or dispensed is considered a sponsor-investigator (§ 312.305(c)(3)). "Licensed physician" and "physician" are used interchangeably in this guidance.

[20] See 21 CFR 312.305(c)(5).

Additionally, the sponsors should maintain accurate contact information to enable rapid communications between FDA and the sponsor and should seek withdrawal of an expanded access IND, with inclusion of a final report, when expanded access treatment has ceased and there is no further intent to treat a patient or patients under the expanded access IND.

B. Expanded Access Submission

Q3. What types of regulatory submissions can be used to obtain expanded access to a drug under the three expanded access categories?

For each category of expanded access, there are two types of regulatory submissions that can be made: (1) an expanded access protocol submitted as a protocol amendment to an existing IND (i.e., an expanded access protocol) or (2) a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use under expanded access (i.e., an expanded access IND).

A sponsor or physician may contact the appropriate FDA review division for consultation regarding the most appropriate type of submission. Additional information about expanded access, including contact information for review divisions, may be found on FDA's website at https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information.

Q4. When should an expanded access protocol submission be used?

An expanded access protocol submission should generally be used only if the sponsor seeking expanded access has an existing IND in effect—typically, such a sponsor is a pharmaceutical company or manufacturer of the drug with an existing IND under which the sponsor is developing the drug for marketing. Only that sponsor, and not a separate sponsor-investigator (e.g., a patient's treating physician), may amend the sponsor's existing IND by submitting a protocol to the IND—unless the IND sponsor gives permission to do so. It is important to note that, under FDA's regulations, FDA generally may not discuss or disclose information about or submitted to a pending IND with any entity other than the sponsor of the IND. Therefore, for expanded access submissions made as a protocol to an existing IND, FDA may not discuss the submission with the patient's treating physician unless that physician is the sponsor of the existing IND.

When there is an existing IND in effect, FDA generally encourages the submission of an expanded access protocol rather than a new expanded access IND because having all expanded access use and clinical trial use consolidated under a single IND may facilitate the administrative and review processes, making it less burdensome for sponsors and FDA.

Q5. When should a new expanded access IND submission be used?

A new expanded access IND submission generally should be used when (1) there is no existing IND in effect for the drug or, more commonly, (2) there is an existing IND in effect for the drug, but the sponsor of the existing IND is not seeking to be the sponsor of the expanded access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's

physician take on the role of sponsor-investigator and submit a separate individual patient IND). See Q7 for more information.

Q6. How does FDA categorize and subcategorize expanded access submissions?

FDA categorizes expanded access submissions as either expanded access INDs or expanded access protocols. In addition, there are three different subcategories of expanded access as explained below. FDA further distinguishes the individual patient expanded access subcategory into emergency and non-emergency individual patient expanded access.

A. Expanded access submissions are subcategorized as follows:

1. Individual Patient Expanded Access, Including for Emergency Use

a. Individual patient expanded access IND

(1) Individual patient expanded access IND for non-emergency use
(2) Individual patient expanded access IND for emergency use

b. Individual patient expanded access protocol

(1) Individual patient expanded access protocol for non-emergency use
(2) Individual patient expanded access protocol for emergency use

2. Intermediate-Size Patient Populations

a. Intermediate-size patient population expanded access IND
b. Intermediate-size patient population expanded access protocol

3. Treatment IND or Treatment Protocol (expanded access for widespread use)

a. Treatment IND
b. Treatment protocol

B. Each subcategory is further defined as follows:

1. Individual Patient Expanded Access, Including for Emergency Use (also referred to as single patient expanded access)

a. Individual patient expanded access IND (also referred to as single patient IND): Expanded access to an investigational drug for treatment use by a single patient submitted under a new IND.

(1) Individual patient expanded access IND for non-emergency use: A type of individual patient IND that provides expanded access to an investigational drug for treatment use by a single patient in a non-emergency situation. Unless FDA notifies

the sponsor (e.g., the patient's physician[21]) that treatment may begin earlier, there is a 30-day period from the date FDA receives the IND before the IND goes into effect and treatment with the drug may begin (§ 312.305(d)(1)).

(2) Individual patient expanded access IND for emergency use: A type of individual patient IND that provides expanded access to an investigational drug for treatment use by a single patient in an emergency situation (e.g., a situation that requires a patient to be treated before a written submission can be made, with treatments expected to have a rapid effect in resolving an acute clinical emergency) submitted under a new IND (§ 312.310(d)). Treatment uses not intended for acute medical emergency (to alleviate an immediate risk of a life-threatening condition or severely debilitating outcome), e.g., those for chronic use to slow progression of disease or for treating chronic symptoms/aspects of a condition, are generally not appropriate as emergency use expanded access requests. For emergency access for a single patient, treatment is initially requested and authorized by telephone (or other means of electronic communication). Treatment may start immediately upon FDA authorization, and the licensed physician or sponsor must agree to submit a written submission (IND) within 15 working days of the initial authorization (§ 312.310(d)(2)).

In an emergency situation, when there is not sufficient time to secure IRB review before beginning treatment, the emergency use of the investigational drug must be reported to the IRB within 5 working days of emergency use, as required under § 56.104(c). The sponsor-investigator should also be aware of their institution's policy regarding IRB review before administration of the drug in such cases. See Q9 for IRB requirements.

b. Individual patient expanded access protocol (also referred to as single patient protocol): Expanded access to an investigational drug for treatment use by a single patient, submitted as a protocol to an existing active IND, generally by the sponsor of the existing IND and, in certain circumstances, by an entity other than the sponsor, such as a licensed physician.

(**1) Individual patient expanded access protocol for non-emergency use**: There is no 30-day period before treatment with the drug may begin, but the protocol must be submitted to FDA and have IRB approval consistent with 21 CFR part 56 (see § 312.305(c)(4)) before treatment may begin.[22] Additionally, if FDA identifies any issues (e.g., safety issue with use of investigational drug) during review of the protocol, FDA may put the protocol on clinical hold.

(2) Individual patient expanded access protocol for emergency use: An emergency use protocol provides expanded access to an investigational drug for

[21] Physicians and sponsors both can submit individual patient expanded access INDs. However, in FDA's experience, licensed physicians typically submit these requests.

[22] See §§ 312.305(d)(2) and 312.30(a).

treatment use by a single patient in an emergency situation. In this case, the sponsor of the existing IND may request authorization to treat the patient before written submission of a protocol to an existing active IND is submitted (§ 312.310(d)). Treatment is initially requested and authorized by telephone (or other rapid means of communication) and may start immediately upon FDA authorization, with a requirement for a written submission (protocol) to FDA within 15 working days of the initial authorization (§ 312.310(d)(2)).

In an emergency situation, when there is not sufficient time to secure IRB review before beginning treatment, the emergency use of the investigational drug must be reported to the IRB within 5 working days of emergency use, as required under § 56.104(c). The sponsor-investigator should also be aware of their institution's policy regarding IRB review before administration of the drug in such cases. See Q9 for IRB requirements.

Contact information for emergency use INDs and protocols is located on FDA's expanded access website at https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information.

2. Intermediate-Size Patient Population Expanded Access

Expanded access to an investigational drug can be provided under an intermediate-size patient population expanded access IND or protocol if FDA determines ***both*** that (in addition to the general expanded access criteria at § 312.305(a) being met):

- There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access (§ 312.315(b)(1))

- There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population (§ 312.315(b)(2))

a. **Intermediate-size patient population expanded access IND**: Expanded access to an investigational drug for use by more than one patient but generally fewer patients than are treated under a typical treatment IND or protocol, submitted under a new IND. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day period from the date FDA receives the IND before treatment with the drug may begin (§ 312.305(d)(1)). IRB review and approval must also be obtained before treatment with the drug may begin (§ 56.103(a)).

b. **Intermediate-size patient population expanded access protocol**: Expanded access to an investigational drug for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol to an existing active IND by the sponsor of the existing IND. There is no 30-day period before treatment with the drug may begin, but the protocol must be

submitted to FDA and have IRB approval, consistent with 21 CFR part 56, before treatment with the drug may begin (§§ 312.305(d)(2) and 312.30(a)).

For more information about intermediate-size patient population expanded access, see Q22 and Q23.

3. Treatment IND or Treatment Protocol

In addition to meeting the criteria in § 312.305(a), expanded access to an investigational drug can only be provided under a treatment IND or protocol if the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or if all clinical trials of the drug have been completed, and the sponsor is actively pursuing, with due diligence, marketing approval of the drug for the expanded access use (§ 312.320(a)).

a. **Treatment IND**: Expanded access to an investigational drug for treatment use by a large (widespread) population, submitted under a new IND. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day period from the date FDA receives the IND before treatment with the drug may begin (§ 312.305(d)(1)). IRB review and approval must also be obtained, consistent with 21 CFR part 56, before treatment with the drug may begin.

b. **Treatment protocol**: Expanded access to an investigational drug for treatment use by a large (widespread) population, submitted as a protocol to an existing active IND by the sponsor of the existing IND. Unlike other expanded access protocols submitted to existing INDs, there is a 30-day period from the date FDA receives the protocol before treatment with the drug may begin unless FDA notifies the sponsor that treatment may begin earlier (§ 312.305(d)(2)(ii)). IRB review and approval must also be obtained, consistent with 21 CFR part 56, before treatment with the drug may begin (§ 312.30(a)).

FDA recommends that the expanded access submission identify the relevant subcategory. In general, FDA authorizes expanded access use within the above-mentioned time frames as stipulated by the regulations for each subcategory of expanded access. However, the time frames when the actual treatment can begin under the different subcategories of expanded access are based on the sponsor having agreed to provide the drug for such use under expanded access. See also Q24, Q25, and Q26.

See Appendix A for a summary of the requirements related to waiting periods and IRB review of the various subcategories and their key distinguishing features.

Q7. What information should be included in an expanded access submission?

An expanded access submission must include all information required by § 312.305(b) and any additional information required for the particular category of expanded access (described in § 312.310(b) for individual patient submissions, in § 312.315(c) for intermediate-size patient

population submissions, and in § 312.320(b) for treatment submissions), either within the submission itself or by reference to an existing IND.

In cases where the sponsor of an existing IND for the drug is not seeking to be the sponsor of the expanded access use, the sponsor of that existing IND may give the sponsor of the expanded access IND permission to reference content in the existing IND to satisfy certain requirements for an expanded access IND submission (§ 312.305(b)). If permission is obtained, the expanded access IND sponsor should then provide to FDA a letter of authorization from the existing IND sponsor (e.g., pharmaceutical company or drug manufacturer) that permits FDA to reference that IND.

FDA expects that reference to an existing IND will typically be used by an expanded access IND sponsor to satisfy the requirements to submit the information described in § 312.305(b)(2)(v) (description of the manufacturing facility); in § 312.305(b)(2)(vi) (chemistry, manufacturing, and controls information); and in § 312.305(b)(2)(vii) (pharmacology and toxicology information).

IND submissions that reference an existing IND generally will include the information described in § 312.305(b)(2)(ii), (iii), (iv), and (viii) and 312.305(b)(3) in the expanded access IND submission. As noted, the expanded access submission must also include the additional information, consistent with 21 CFR part 312, subpart I, that may be required for the specific category of expanded access.

Q8. What forms are used for expanded access submissions?

The licensed physician[23] acting as a sponsor-investigator may submit an individual patient expanded access IND using Form FDA 3926 [8,24] (Individual Patient Expanded Access—Investigational New Drug Application (IND)), which, when completed (including attachments, if appropriate), constitutes the individual patient IND submission. Form FDA 3926 provides a streamlined alternative to Form FDA 1571 (Investigational New Drug Application (IND)) for physicians submitting an IND for treatment of an individual patient under expanded access, including for emergency use. Sponsor-investigators may either download Form FDA 3926 directly from the FDA website to complete and then submit to FDA, or they may use a streamlined tool available online (eRequest app) to help them complete and submit Form FDA 3926.[25]

Individual patient expanded access INDs, including for emergency use, may also be submitted by a licensed physician acting as a sponsor-investigator using Form FDA 1571, which is a

[23] A licensed physician who submits Form FDA 3926 to request individual patient expanded access for a patient is considered to be acting as a sponsor-investigator. "Licensed physician" and "physician" are used interchangeably in this guidance.

[24] The time required to complete this form is estimated to average 45 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information.

[25] Reagan Udall Foundation's Expanded Access eRequest app is a streamlined tool for the physicians to submit expanded access requests online, available at https://erequest.navigator.reaganudall.org/#/home.

transmittal form that accompanies the IND and provides information to identify the type of submission and its contents.

Form FDA 1571 should accompany the submissions for any of the following: (1) individual patient protocols submitted to an existing IND, (2) intermediate-size patient population INDs and protocols, and (3) treatment INDs and protocols. The most current version of all FDA forms and accompanying instructions, if available, can be downloaded from the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

The following table illustrates which form may be used for each type of submission:

Table 1. Acceptable Expanded Access Submission Forms

	Form FDA 3926	Form FDA 1571
Individual patient IND submitted by a licensed physician[#^]	✓	✓
*Individual patient IND for emergency use submitted by a licensed physician[#]	✓	✓
Individual patient protocol		✓
Individual patient protocol for emergency use		✓
Intermediate-size patient population IND		✓
Intermediate-size patient population protocol		✓
Treatment IND		✓
Treatment protocol		✓

[#] In these cases, the licensed physicians may use either of these forms to submit the IND to FDA.
^ A commercial sponsor of an individual patient expanded access IND should use Form FDA 1571. Form FDA 3926 is not intended for use by commercial sponsors.
* When using Form FDA 3926 for individual INDs for emergency use, the box in Field 10.b (Request for authorization to use alternative IRB review procedures) should not be selected. See Q9 in this guidance.

Q9. Is IRB review and approval required for all expanded access categories?

Except for emergency expanded access use when there is not sufficient time to secure prospective IRB review before beginning treatment (see Q6, B.1.a.(2) and B.1.b.(2)), an investigator treating a patient with an investigational drug under expanded access is responsible for obtaining IRB review[26] and approval consistent with 21 CFR part 56 before treatment with

[26] An IRB (institutional review board) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to ensure that the rights and welfare of human subjects are

the investigational drug may begin, regardless of whether the expanded access protocol is submitted in a new IND or to an existing IND (§ 312.305(c)(4)). Part 56 requires, among other things, that the IRB review the expanded access use at a convened IRB meeting at which a majority of the members are present (full IRB review) (§ 56.108(c)).

Non-emergency individual patient expanded access IND: Upon request, FDA intends to allow for waivers of the requirement under § 56.108(c) for review and approval at a convened IRB meeting for individual patient expanded access INDs in cases when the IRB chairperson or another designated IRB member provides concurrence with the proposed treatment use under expanded access before treatment begins. In these cases, the review of the individual patient expanded access use is conducted by the IRB chairperson (or designated IRB member) and would not be reviewed at a convened IRB meeting or through expedited review procedures. Rather, the IRB chair or designee reviews the relevant documents as determined by the IRB's Standard Operating Procedures. The decision to concur or not with the request to approve the individual patient expanded access IND (and/or any questions and responses) is documented by the IRB chair or designee. FDA concludes that such a waiver is appropriate for individual patient expanded access INDs for the initial submission, any amendments (e.g., for change in the use or duration of treatment) to the IND, and, if applicable, continuing review. FDA intends to consider a completed Form FDA 3926 with the box in Field 10.b selected and the form signed by the physician to be a request for a waiver under § 56.105 of the requirements in § 56.108(c), which relates to full IRB review. When a waiver is requested in this manner, the physician does not receive notice from FDA indicating that the waiver is granted. Alternatively, the physician may request a waiver separately in an amendment to the IND. When the request for waiver is accomplished by submission of a separate waiver request, FDA issues a response to the waiver request.

If a physician submits an individual patient expanded access IND using Form FDA 1571 and wishes to request a waiver from full IRB review, a separate waiver request under § 56.105 of the requirements in § 56.108(c) should be submitted with the application. FDA issues a response to the waiver request in this situation.

If the initial protocol under an individual patient expanded access IND was reviewed and approved by the full IRB but the physician would like any amendments or the continuing review to be conducted by the IRB chairperson or the chairperson's designee instead, the physician may amend the IND with a correspondence that clearly indicates the intent of the amendment (to change the approach for continuing IRB review of the expanded access protocol) and that includes a request for waiver under § 56.105 of the requirements in § 56.108(c). As described previously, FDA intends to consider a completed Form FDA 3926 with the box in Field 10.b selected and the form signed by the physician to be a request for such a waiver. Alternatively,

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protected, including by determining that informed consent is obtained in accordance with and to the extent required by Federal requirements. Institutions may have their own IRB to oversee human subjects research conducted within the institution or by the staff of the institution. If the patient's physician does not have access to a local IRB, an independent IRB may be used. The Department of Health and Human Services' Office for Human Research Protections maintains a database of registered IRBs. Go to https://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc and select "Advanced Search." Enter your state to find registered IRBs in your area. For more information, see https://www.fda.gov/news-events/public-health-focus/expanded-access.

the physician may amend the IND with a separate request for waiver of continuing IRB review by the full IRB if Form FDA 1571 was used or if Field 10.b in Form FDA 3926 was not checked.

Emergency individual patient expanded access IND: FDA authorization is required before initiation of treatment (§ 312.310(d)). However, emergency expanded access use is exempted from obtaining full IRB approval before initiation of treatment (§ 56.104(c)) provided that the IRB is notified of the emergency expanded access use within 5 working days of emergency use. Following receipt of notification of such emergency use, the IRB should follow its documented written procedures[27] for review of emergency expanded access use. A physician may choose to use Form FDA 3926 for submitting the emergency expanded access application. In such emergency expanded access cases, the box in Field 10.b on Form FDA 3926 should be left *unchecked* because Field 10.b is intended for requesting a waiver to obtain concurrence by the IRB chairperson or by a designated IRB member, in lieu of full IRB review, *before the treatment use* begins for non-emergency individual patient expanded access.

Intermediate IND/Protocol and Treatment IND/Protocol: The Agency believes a waiver is not appropriate for intermediate and treatment INDs and protocols. Section 312.23(a)(1)(iv) requires that an IND submission include sponsor commitment that an IRB will be responsible for the initial and continuing review of the studies under an IND.

Q10. Is a physician participating in an expanded access protocol sponsored by another entity (e.g., manufacturer of the drug) required to obtain local IRB review and approval?

The sponsor of the expanded access protocol (e.g., manufacturer of the drug) may arrange for IRB review and approval of the protocol and the participating physicians with a single IRB of record. If the sponsor has arranged for IRB review and approval of the protocol and participating physicians, the physician may not be required to obtain separate local IRB review and approval. A physician associated with an institution should verify that the sponsor has obtained IRB review and approval of the protocol and will provide oversight of the participating physician. The physician should consult their institution on their policy in these situations. Some institutions may require that their physicians obtain review and approval from the institution's IRB as well. If the local IRB cedes review to the single IRB of record, this should be documented in an agreement signed by the parties. Physicians who are not associated with an institution should verify with the sponsor that they are included in the IRB approval. If they are not (e.g., they join the expanded access protocol after the initial IRB approval), they should work with the sponsor to ensure inclusion in the IRB approval prior to initiating the protocol.

Q11. Can the same drug be used in an emergency situation at the same institution more than once? If so, is prospective IRB review required for the subsequent expanded access emergency use?

There can be more than one expanded access emergency use of the same drug at the same institution. For expanded access use authorized under emergency procedures, the emergency use

[27] See the guidance for institutions and IRBs *Institutional Review Board (IRB) Written Procedures* (February 2025).

must be reported to the responsible IRB within 5 working days of initiation of treatment (§ 56.104(c)). 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 (§ 56.104(c)). 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[28] 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 (§ 56.104(c)).

Q12. Are expanded access submissions subject to informed consent requirements?

Yes. FDA considers expanded access use of an investigational drug to meet the definition of clinical investigation in 21 CFR 50.3(c) since an IND or protocol to an existing IND must be submitted to provide investigational drugs under expanded access (§ 312.305(b)). Therefore, expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50, unless one of the exceptions found in part 50 applies.[29] Investigators treating a patient or patients with an investigational drug under expanded access are responsible for ensuring that the informed consent requirements of part 50 are met (§ 312.305(c)(4)).[30] One of the purposes of informed consent is to ensure that patients are informed that they will be treated with an investigational product and that there may be uncertainty about the safety and effectiveness of the product.

Please note that the additional safeguards regarding informed consent for children in clinical investigations found in 21 CFR part 50, subpart D, also apply to expanded access submissions for the treatment of children. Among other things, a clinical investigator must obtain permission from the parent(s) or guardian(s) when a child is enrolled in a clinical investigation (21 CFR 50.55(e)). The parental/guardian permission form must address the required elements of consent, as well as appropriate additional elements (see 21 CFR 50.25) to allow the parent(s) or guardian(s) to make an informed decision. If the IRB determines that the child is capable of providing assent, adequate provisions must be made for soliciting assent from the child (21 CFR 50.55(a)). Assent means a child has provided affirmative agreement to participate in a clinical investigation; mere failure to object should not be construed as assent (21 CFR 50.3(n)).[31]

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[28] In this guidance, reference to a request being denied means that such a request is put on clinical hold (§ 312.42(b)(3)).

[29] See 21 CFR part 50.

[30] For additional information on the informed consent process, see the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023).

[31] For FDA's recommendations on assent process for children, see the draft guidance for industry, sponsors, and IRBs *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022). When final, this guidance will represent FDA's current thinking on this topic.

Q13. What information should be included in the informed consent document for obtaining a patient's consent for treatment under individual patient expanded access?

The consent form must contain information set out in §§ 50.20 and 50.25 to allow the patient to make an informed decision about receiving experimental treatment.[32] FDA is sharing a template (see the Appendix B) that investigators may find helpful for obtaining informed consent from patients for individual patient expanded access. Physicians and institutions may use this template to model their forms for obtaining consent from patients under expanded access.

Q14. Under the informed consent regulations, informed consent documents must include "[a] statement that the study involves research." Is that appropriate for informed consent documents used for expanded access?

It is acceptable for informed consent documents used for expanded access to contain a statement that treatment under expanded access involves research. As an alternative and given that the drug used under expanded access is investigational, FDA 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 disease or condition, to also satisfy the requirement under § 50.25(a)(1) that the informed consent provide a statement that the use of the product involves research.

C. Individual (or Single) Patient Expanded Access

Q15. Who can make a submission for individual patient expanded access?

The sponsor of an existing IND under which a drug is being developed (e.g., a pharmaceutical company or manufacturer of the investigational drug) or a licensed physician may make an individual patient expanded access submission (§ 312.310(b)(1)).

The sponsor of an existing IND can submit an individual patient expanded access protocol to its existing IND. In this scenario, the sponsor of the existing IND is also the sponsor of the expanded access protocol, and the patient's physician is the investigator for the expanded access protocol.[33] The term investigator is used because the drug is investigational, but the term does not denote the licensed physician's or patient's involvement in a clinical trial.

Although a sponsor of an existing IND could submit a new individual patient expanded access IND and cross-reference the information in its existing IND, FDA prefers for sponsors to submit an individual patient expanded access protocol to an existing IND. Having all clinical trials and

[32] See the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023).

[33] For the purposes of this guidance, it is assumed that the patient's physician is the same person as the investigator. The pharmaceutical company or drug manufacturer may designate the investigator role to a physician who may not be the physician of the patient. In this scenario, it is the responsibility of the sponsor-appointed investigator to collect all necessary information from the patient's physician to make decisions about treatment and to fulfill the responsibilities of an investigator.

expanded access for a drug under a single IND eases the administrative burden and facilitates the review process, making it less burdensome for sponsors and FDA. In this scenario, the sponsor of the existing IND is also the sponsor of the expanded access protocol, and the patient's physician is the investigator for the expanded access protocol.

An individual patient's physician can submit an individual patient expanded access IND for their patient. In this scenario, when the patient's physician submits an expanded access IND, the physician is both the sponsor and the investigator—in other words, the physician is considered a sponsor-investigator[34] for the purposes of part 312. The physician may satisfy some of the expanded access submission requirements by referring to information in an existing IND if the physician obtains permission from the sponsor of the existing IND (see Q7). If the physician obtains this permission from the sponsor of the existing IND, the physician should provide to FDA the letter of authorization from the sponsor of the IND that permits FDA to reference the sponsor's IND.

In cases where it is not possible to obtain a letter of authorization (e.g., the entity supplying the drug does not have an IND filed with FDA), the physician should contact the relevant FDA review division to determine what information is needed per § 312.305 to support the expanded access submission. The physician should also contact the FDA review division if the individual patient expanded access IND is for an approved drug where availability is limited by a REMS. The physician should then submit an individual patient expanded access IND to the appropriate FDA review division and may choose to use Form FDA 3926.[35] Contact information for review divisions may be found on FDA's website at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

If the sponsor of the existing IND (e.g., the pharmaceutical company or drug manufacturer) does not authorize reference to the IND, the physician sponsoring the expanded access IND must include in the IND all the information (e.g., relevant preclinical and chemistry, manufacturing, and controls information) required to support the expanded access IND (§§ 312.305 and 312.310).

A patient's physician may not submit an individual patient expanded access protocol to an existing IND for which the physician is not the sponsor.

Regardless of who sponsors an individual patient expanded access protocol or expanded access IND, the patient can obtain expanded access to the investigational drug only through treatment by a licensed physician (§ 312.310).

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[34] See § 312.305(c)(3).

[35] Form FDA 3926 and accompanying instructions are available on FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Q16. What are the roles of the patient's physician and FDA in determining if expanded access for an individual patient is appropriate?

FDA may permit expanded access to a drug for an individual patient when the criteria in § 312.305(a) (applicable to all types of expanded access) and the criteria in § 312.310(a) (specific to individual patient expanded access) are met. For these criteria to be met, both the patient's physician and FDA must make certain determinations.

The patient's physician must determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition (§ 312.310(a)(1)). The physician should make this determination based on the information about the drug available to the physician and the physician's knowledge of the patient's clinical situation. FDA acknowledges that there is often limited information available to physicians about the risks and benefits of an investigational drug and no practical way to provide the physician the information at FDA's disposal (information in an IND is typically proprietary and generally can only be disclosed to a member of the public with consent of the pharmaceutical company or drug manufacturer).

Therefore, as with all types of expanded access, FDA must determine, based on the information available to FDA, that the potential benefit justifies the potential risks of the treatment use with the drug and that those risks are not unreasonable in the context of the disease or condition to be treated (§ 312.305(a)(2)). FDA may have access to more information about the investigational drug than the patient's physician or the drug company and evaluates the potential benefits and risks of therapy considering the information provided by the physician. Therefore, FDA may reach a different conclusion than the physician, based on the information available to the Agency about the investigational drug. As noted previously, in most cases, FDA will not be able to share the information about the investigational drug on which its conclusion is based.

To authorize the expanded access use, FDA must also determine (1) that the patient has a serious or life-threatening disease or condition and has no other comparable or satisfactory therapeutic options (§ 312.305(a)(1)); (2) that providing expanded access will not interfere with development of the drug for the expanded access use (§ 312.305(a)(3); see Q28); and (3) that the patient cannot obtain the drug under another IND or protocol (e.g., in a clinical study of the drug) (§ 312.310(a)(2)).

Q17. What are some of the reasons for FDA to deny a request for individual patient expanded access when previous requests for the same drug for the same or a similar use have been permitted?

FDA treats each request for individual patient expanded access to a drug as a unique clinical situation and evaluates the risks and benefits of the requested expanded access use based on that clinical situation. Even when there are two or more individual patient expanded access requests for patients with the same disease or condition, there may be significant differences in the clinical presentation of the disease or condition that make the risks acceptable for one patient but not for another. For example, a patient may have a different stage of the disease or different tumor type than previous patients who were permitted expanded access to the drug and,

therefore, may have a different benefit-risk assessment. Similarly, a patient may have a comorbid condition not present in previous patients who obtained expanded access that would make the risk unacceptable. FDA may also become aware of new safety signals or information about effectiveness that changes the benefit-risk assessment such that the risk is no longer acceptable for the patient. In cases such as these, individual patient expanded access for additional patients might be denied.

There also may be other reasons for denying expanded access. For example, a patient seeking expanded access may be able to enroll in a clinical trial that was not accessible to a previous patient who was granted expanded access (e.g., because the previous patient did not meet the inclusion criteria for the trial, or the trial was geographically inaccessible to the previous patient).

FDA could also have become aware since authorizing previous requests for expanded access that expanded access is impeding the clinical development of the drug and, on that basis, place further requests for expanded access on clinical hold (§ 312.42(b)(3)) (see Q28).

Q18. How does FDA address individual patient expanded access applications for treatment with multiple courses of therapy or treatment of a chronic condition?

Under § 312.310(c)(1), individual patient expanded access is generally limited to a single course of therapy for a specified duration. However, as reflected in § 312.310(c)(1), FDA may authorize multiple courses of therapy or chronic therapy for individual patient expanded access, including authorizing individual patient expanded access to treat a chronic disease or condition that requires extended treatment. FDA generally authorizes such individual patient expanded access when the circumstances of the treatment are well-defined and reasonable considering the available evidence to support use of the drug. The patient's physician (as the investigator) proposes the full course of treatment when filing the request for expanded access. To fairly weigh the risks and benefits of a drug for use for individual patient expanded access, FDA believes the planned course of therapy should be well-defined because it will usually be necessary to consider the planned dose and duration of therapy in relation to what is known about the occurrence of toxicity for that dose and duration of therapy.

FDA does not usually authorize expanded access for an unspecified duration. FDA typically authorizes expanded access for a specified extended duration for the treatment of a chronic condition when the patient's condition and the information available about the safety of the drug supports an extended duration of treatment. For example, FDA may authorize expanded access of extended duration for a drug being developed to treat multiple sclerosis or other types of progressively debilitating neuromuscular disease if there is evidence that the drug must be administered chronically to slow the progression of the disease and if the information available about the safety of the drug supports an extended duration of treatment. If expanded access use is authorized for an extended duration, FDA may require the sponsor to monitor the individual patient expanded access use through the extended duration (see § 312.310(c)(3)).

Q19. When should individual patient expanded access using the emergency procedures in § 312.310(d) be requested?

Section 312.310(d) states that FDA may authorize expanded access for an individual patient without a written submission if there is "an emergency that requires the patient to be treated before a written submission can be made." The licensed physician or sponsor, however, must agree to submit an expanded access IND or protocol within 15 working days of FDA's authorization of the emergency use (§ 312.310(d)(2)). Under this regulation, FDA considers it appropriate to request individual patient expanded access using the emergency procedures described in § 312.310(d) when treatment of the patient must occur within a very limited number of hours or must occur before the next business day after regular business hours. FDA intends to authorize expanded access using the emergency procedures only when the standard for emergency use described in § 312.310(d) has been met. If FDA determines that the standard described in § 312.310(d) has not been met but the situation qualifies for expanded access, FDA will accept it as a non-emergency individual patient IND once the application is officially submitted. In such case, the sponsor can treat the patient when the IND goes into effect 30 days after FDA receives the IND (unless the IND is put on clinical hold, i.e., is not allowed to proceed) or on earlier notification by FDA (§§ 312.40 and 312.305(d)(1)).

Q20. Can a pharmaceutical company or the drug manufacturer that is developing the drug for marketing request individual emergency expanded access to its investigational drug to treat multiple patients?

Yes, however, a separate emergency use IND or protocol would need to be submitted for each patient to be treated. If there is an existing IND, the sponsor should submit protocols to the existing IND rather than submit multiple new INDs. The pharmaceutical company or drug manufacturer can submit multiple such emergency use INDs or protocols to its existing IND. An amendment to an individual patient IND to treat additional patients is not acceptable. However, if multiple emergency expanded access requests for similarly situated patients are anticipated, FDA may request that a sponsor submit an intermediate-size patient population expanded access IND or protocol or treatment expanded access IND or protocol, as appropriate (see Q22).

D. Intermediate-Size Patient Population and Treatment INDs and Protocols

Q21. Can there be more than one intermediate-size patient population or treatment expanded access IND or protocol for a particular drug for the same disease or condition?

When multiple patients with the same disease or condition seek expanded access to a particular drug and the relevant criteria for expanded access are met, FDA believes that it is generally most efficient to consolidate expanded access in a single intermediate-size patient population or treatment expanded access IND or protocol (see Q22). If the drug is being developed, FDA believes it is most efficient if the pharmaceutical company or the drug manufacturer that is developing the drug for marketing is the sponsor of a single intermediate-size patient population or treatment expanded access protocol (see Q22). However, the regulations do not preclude the possibility of authorizing more than one expanded access IND or protocol, with different

sponsors or sponsor-investigators, for a drug for the same disease or condition. Thus, there may be situations in which there are multiple expanded access INDs or protocols for a drug for the treatment of the same disease or condition. FDA expects these situations to arise infrequently.

Q22. When is it appropriate to request expanded access for multiple patients using an intermediate-size patient population expanded access IND or protocol rather than a treatment IND or protocol?

FDA regulations do not impose specific numerical limitations for when an intermediate-size patient population expanded access IND or protocol (as opposed to a treatment IND or protocol) may be appropriate. This determination generally depends on the following two factors:

1. *Whether the drug is under development for marketing for the same indication as the expanded access use*

   If the drug is not being developed for marketing for the same indication as the expanded access use and the expanded access IND or protocol is intended to treat more than a single patient, expanded access would be provided under an intermediate-size patient population expanded access IND or protocol rather than a treatment IND or protocol. Expanded access to an investigational drug to multiple patients can only be provided under a treatment IND or protocol if the drug is being developed for marketing for the same indication as the expanded access use (see § 312.320(a)(2)). When the investigational drug is being developed for marketing, intermediate-size patient population expanded access is used earlier in development than treatment INDs or protocols. Also, if FDA determines clinical development of the drug is essentially complete (i.e., the clinical trials to support marketing approval of the investigational drug have ended) and the intent of the expanded access is to bridge the gap between completion of the clinical trials and marketing of the drug (to ensure that treatment is not interrupted and to expand treatment to additional patients), the expanded access, regardless of the number of patients expected to be treated, would generally be designated as a treatment IND or protocol.

2. *Size of the patient population*

   The second factor important to a determination of whether expanded access is provided under an intermediate-size patient population expanded access IND or protocol (as opposed to a treatment IND or protocol) is the size of the patient population. In general, intermediate-size patient population expanded access is intended to accommodate population sizes smaller than the large populations typical of treatment INDs or protocols. However, as noted in the preceding paragraph, if FDA determines clinical development is complete and the intent of the expanded access IND or protocol is to bridge the gap between the completion of clinical trials and marketing of the drug, expanded access would generally be provided under a treatment IND or protocol, regardless of the intended size of the patient population. Similarly, if the drug is not being developed for marketing for the expanded access use, expanded access would generally be provided under an intermediate-size patient population IND or protocol,

regardless of the size of the patient population, as long as it is intended to treat more than a single patient.

Separate single patient INDs may be combined into a single intermediate-size patient population protocol when feasible and practical, at the request of the sponsor or FDA. Adding patients to an intermediate-size patient population protocol can reduce paperwork and simplify IRB review. In such cases, any number of patients beyond one might be reasonable for an intermediate-size patient population protocol. FDA may be consulted on how to consolidate single patient expanded access under an intermediate-size patient population expanded access protocol. When a growing number of eligible patients might benefit from treatment access under an intermediate-size patient population protocol, a treatment IND or protocol may be appropriate. (See Q23.)

Q23. The regulations in § 312.315(d)(1)(iii) state that as enrollment in an intermediate-size patient population expanded access IND or protocol increases, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.320 (i.e., to transition the intermediate-size patient population expanded access IND or protocol to a treatment expanded access IND or protocol). When would FDA make such a determination and how would such a transition be carried out?

FDA anticipates that there would ordinarily be a seamless transition from intermediate-size patient population expanded access to expanded access under a treatment IND or protocol at the point when the evidence is sufficient to support the treatment IND or protocol, when there is adequate progress with drug development, and when the sponsor is willing to make the drug available to a potentially larger patient population under a treatment IND or protocol. Although there is a 30-day period before treatment can begin under the new treatment IND or protocol, as required by the regulations, the review division can act sooner, and FDA may notify the sponsor that treatment may begin earlier (§§ 312.40 and 312.305(d)).

For such a transition, all patients currently receiving treatment with the investigational drug would continue treatment under the intermediate-size patient population expanded access IND or protocol, as appropriate, until they transition to the treatment IND or protocol (to ensure that treatment is not interrupted). Once all patients in the intermediate-size patient population expanded access IND or protocol are receiving their treatment under the new treatment IND or protocol, the sponsor should request that the intermediate-size patient population expanded access IND or protocol be withdrawn.

E. Time Frame for Beginning Treatment Use Under an Expanded Access IND or Protocol

For clarity, the time frames mentioned here for when treatment use can begin under the different subcategories of expanded access are based on the sponsor having agreed to provide the drug for such use under expanded access.

Q24. When can treatment begin under emergency use expanded access INDs or protocols?

For an emergency use, treatment may begin immediately upon authorization (usually provided by telephone or other rapid means of communication) by the FDA reviewing official (§§ 312.310(d) and 312.305(d)(2)(i)), with a requirement for a written submission (IND/protocol) to FDA within 15 working days of the initial authorization (§ 312.310(d)(2)). As explained in Q6 and Q9, FDA anticipates that for expanded access uses authorized under the emergency procedures, there typically will not be time to obtain prior IRB approval of the use. In such cases, the emergency use must be reported to the IRB within 5 working days of initiation of treatment (§ 56.104(c)).

Q25. When can treatment begin under expanded access INDs not for emergency use?

When an expanded access IND (not for emergency use) is submitted, the treatment use of the drug may begin when the IND goes into effect and IRB approval has been obtained consistent with 21 CFR part 56 (see § 312.305(c)(4)). As is true for any new IND, an expanded access IND goes into effect 30 days after FDA receives the IND (unless the IND is put on clinical hold, i.e., is not allowed to proceed) or on earlier notification by FDA (§§ 312.40 and 312.305(d)(1)).

Q26. When can treatment begin under expanded access protocols not for emergency use?

For an individual patient or intermediate-size patient population expanded access protocol, expanded access to the drug can begin once the expanded access protocol has been submitted to FDA and has been approved by an IRB (§§ 312.30(a) and 312.305(d)(2)). For a treatment protocol, however, expanded access may not begin until 30 days after FDA receives the protocol (or on earlier notification by FDA (§ 312.305(d)(2)(ii)) and IRB approval has been obtained consistent with 21 CFR part 56 (see § 312.305(c)(4)).

F. General Questions

Q27. Can FDA require a sponsor to provide expanded access to its drug if FDA authorizes the expanded access?

No. FDA cannot compel a sponsor to provide expanded access to its drug. A sponsor provides expanded access to its drug voluntarily.

Q28. How does FDA determine that authorizing expanded access to a drug will not interfere with clinical trials or drug development?

Under § 312.305(a)(3), to authorize any category of expanded access, FDA must determine that expanded access to the drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the drug for the expanded access use. Generally, to receive the drug under an expanded access IND or protocol, patients

should be ineligible or otherwise unable (e.g., geographically unable to access a study site) to enter ongoing clinical trials.

FDA believes that expanded access INDs or protocols that treat larger patient populations generally have high potential to interfere with clinical investigations or drug development because of their greater potential to interfere with recruiting patients for the clinical investigation or investigations. Even a series of individual expanded access requests for an investigational drug for treatment of a rare disease, especially one in which the prevalence is measured in the hundreds or even thousands of patients, could potentially impact a clinical development program.

For FDA to determine whether an expanded access use will interfere with clinical investigations or drug development, FDA may ask the sponsor to provide additional information if FDA cannot make a determination based on the information the sponsor previously provided. For example, before authorizing a treatment IND for a drug for which clinical trials are ongoing, FDA may ask the sponsor to explain (1) how the sponsor will ensure that the treatment IND will not interfere with accrual of patients in the clinical trials and (2) how the sponsor will determine whether interference with clinical development is occurring, if such information is not provided in the expanded access submission. More specifically, FDA may ask the sponsor to submit to its IND a comprehensive investigational plan with a timetable and milestones (if it has not done so already) so that FDA can periodically assess whether the treatment IND is affecting accrual of patients in the clinical trials or other parameters related to the pace of drug development. If FDA then determines that the ongoing treatment IND is interfering with clinical trials or drug development or that the sponsor is not pursuing, with due diligence, marketing approval for the expanded access use, FDA could place the treatment IND on clinical hold (§ 312.42(b)(3)(ii)).

The potential for expanded access to interfere with clinical trials/drug development is also high for rare disease drug development programs, where the number of subjects available for participation in a clinical trial is limited. This potential is highest early in development and decreases as development progresses. In general, for rare disease drug development, well-controlled clinical trials should be initiated before patients are treated with the drug under expanded access, and expanded access should be sought only for those patients who are truly not eligible for or are unable to participate in those well-controlled trials. Sponsors developing drugs for the treatment of a rare disease should consider study designs that help to minimize barriers to trial participation such as broad inclusion criteria, virtual or at-home visits, or utilizing health facilities that may be closer in proximity to potential subjects.[36] Once the trials required by FDA to support a marketing application have been completed, there is little risk for interference with drug development, and broader expanded access may be considered.

Q29. What data and information must sponsors submit as follow-up for active expanded access INDs or protocols?

As with any IND, in all cases of expanded access, sponsors are responsible for complying with expedited IND safety reporting requirements under § 312.32 and for submitting annual reports (when the IND or protocol continues for 1 year or longer) under § 312.33 (see § 312.305(c)). To

[36] See the guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

comply with expedited IND safety reporting requirements under § 312.32(c)(1)(i), the sponsor must report any suspected adverse reaction that occurs during treatment and that is both serious and unexpected. Further, the sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. Data and information on expanded access protocols submitted to an existing IND may be provided in the annual report for the IND. As relevant to this question, the regulations in § 312.10(c)(2) provide that, at the conclusion of treatment for individual patient expanded access, the sponsor must provide to FDA a written summary of the results of the expanded access use, including adverse effects. FDA considers adverse effects to have the same meaning as adverse events as defined in § 312.32(a).[37]

Q30. Why does FDA review adverse event data for expanded access INDs?

From a public health perspective, early identification of important adverse events is beneficial. For example, a relatively rare adverse event might be detected during expanded access use, or such use might contribute safety information for a population not exposed to the drug in clinical trials. FDA is aware of a small number of cases in which clinical safety data from expanded access treatment were used to help assess the risks and benefits of the drug. In a very small number of cases, adverse event information from expanded access has contributed to safety information reflected in the FDA-approved labeling for a drug product. FDA is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug. FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted and will evaluate any adverse event data obtained from an expanded access submission within that context. For example, FDA reviewers recognize the following:

(1) Expanded access treatment generally occurs outside a controlled clinical trial setting.

(2) Patients who receive a drug through expanded access may have a more advanced stage of the disease or condition than patients participating in a clinical trial.

(3) Patients who receive a drug through expanded access may be receiving other therapies for their disease or condition at the same time as the drug they are receiving through expanded access.

(4) Patients who receive a drug through expanded access may have one or more comorbidities.

All of these factors make it difficult to attribute a particular adverse event to the expanded access treatment. Moreover, it is very rare for FDA to place an IND on clinical hold due to adverse events observed in expanded access treatment.

[37] Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. See § 312.32(a).

Q31. Can FDA consider an IND or protocol submission to be an expanded access submission and identify and review it as such, even though the applicant does not identify it as an expanded access submission?

Yes. For example, FDA intends to evaluate whether proposals for studies described as open-label safety studies should be considered treatment INDs or protocols. The goal of an open-label safety study is to better characterize the safety of a drug late in its development.

However, in practice, many studies that are described as open-label safety studies have characteristics that appear to be more consistent with treatment INDs or protocols. If an IND or protocol describes an open-label study that provides for broad expanded access to an investigational drug in the later stages of development but lacks planned, systematic data collection and a design adequate to meaningfully evaluate a safety issue, FDA will generally consider the submission to be a treatment IND or protocol. In the event that a protocol is not submitted as an expanded access protocol but is designated as such by FDA, the review division will notify the sponsor of the designation.

Q32. What is the difference between an expanded access protocol and a continuation or open-label safety protocol?

A continuation protocol (also referred to as an extension trial) describes a trial in which patients are allowed to remain on an investigational drug or to cross over to an investigational drug from placebo or active control following conclusion of the randomized phase of a trial. An open-label safety study is an unblinded study in which safety data are collected. The primary purpose of both continuation and open-label safety protocols, in contrast to expanded access protocols, is to obtain safety data on the investigational drug. The conduct of continuation and open-label safety protocols differs from that of expanded access protocols in that (1) participation in open-label safety and continuation protocols is usually limited to specific, named institutions/centers; (2) participating investigators in continuation or open-label safety protocols are already identified and trained to collect appropriate safety data; and (3) in the case of a continuation trial, participants are typically limited to those in the original randomized controlled trial.

A protocol for which the primary intent is treatment of patients and for which enrollment is limited to patients who participated in the clinical trials to support approval of the investigational drug is considered a continuation protocol and not an expanded access protocol, even though the primary intent is treatment. For such protocols, access to the investigational drug is not *expanded* beyond those patients who participated in the clinical trials. The design and requirements for a continuation protocol for which the primary purpose is treatment of patients—and not collection of additional safety or other data—will generally be much simpler with fewer requirements than those for a continuation protocol for which the primary purpose is collection of additional safety or other data.

Q33. If a sponsor continues to provide its investigational drug for treatment use under its IND to a patient who was enrolled in a clinical trial but subsequently does not meet the prior inclusion criteria, is that considered expanded access (i.e., is the sponsor

expected to make an expanded access submission to continue to provide the drug to that patient)?

In general, if a patient is already enrolled in a clinical trial (designed to further the development of or determine the safety and/or effectiveness of an investigational drug) and the patient's results are to be included in the analysis of the investigational drug, the continued administration of the investigational drug to that patient is not considered expanded access.[38]

Q34. If a sponsor provides its investigational drug for treatment use under its IND to a patient who does not meet inclusion criteria for their trial and is not enrolled in the trial, is that considered expanded access?

In general, if a patient is not enrolled in a clinical trial but is provided access to the investigational drug for the purposes of treating the patient, treatment of that patient with the investigational drug is considered expanded access to the investigational drug. The requirements for expanded access, including submission of an expanded access IND or protocol (as appropriate) to FDA, would apply.

Q35. May treatment with two or more investigational drugs be requested and authorized under a single expanded access IND or protocol, or may an individual patient participate in more than one expanded access IND or protocol (e.g., be enrolled in two different treatment INDs)?

Yes. A single expanded access IND or protocol may involve treatment with more than one investigational drug, and a patient may be enrolled in more than one expanded access IND or protocol. When expanded access to two or more investigational drugs is appropriate to treat a single disease and the relevant criteria are met, it is most efficient to provide expanded access to the multiple investigational drugs under a single expanded access IND or protocol, rather than to provide expanded access by having a patient enroll in two or more separate expanded access INDs or protocols (one for each drug). Management of the patient's disease, treatment, and the collection of information about the therapy is likely to be better coordinated under a single expanded access IND or protocol.

Q36. How can manufacturers and distributors comply with the requirement to make their expanded access policies readily available to the public?

The enactment of the Cures Act added section 561A to the FD&C Act.[39] This section requires a manufacturer or distributor of one or more investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions to make its policy for evaluating and responding to expanded access requests submitted under section 561(b) of the FD&C Act (i.e., expanded access policy) readily available to the public, such as by posting the policy on a publicly available website (e.g., the manufacturer's website, the Reagan-Udall Foundation

[38] This is commonly known as a protocol exception and would be covered under the existing IND.
[39] See 21 U.S.C. 360bbb-0.

Expanded Access Navigator web page (see Q38)).[40] Manufacturers and distributors of investigational medical devices are not required to comply with section 561A of the FD&C Act.

The expanded access policy must include all of the following:[41]

- Contact information for the manufacturer or distributor to facilitate communication about expanded access requests submitted under section 561(b) of the FD&C Act
- Procedures for submitting expanded access requests
- The general criteria the manufacturer or distributor will use to evaluate individual patients' expanded access requests and for responses to such requests
- The length of time the manufacturer or distributor expects will be needed to acknowledge receipt of such requests
- A hyperlink or other reference to the clinical trial record containing information about expanded access availability for the drug that is required to be submitted to ClinicalTrials.gov [42]

FDA recommends that the pharmaceutical company or the drug manufacturer that is developing the drug for marketing make its expanded access policy publicly available, rather than the distributor. Posting the expanded access policy on its own website will fulfill the requirement of making the policy available to the public.[43] If a pharmaceutical company or the drug manufacturer is developing multiple investigational drugs, it may have one general expanded access policy that applies to all applicable products and should make such general policy publicly available. However, if it has different expanded access policies for different investigational drugs, each expanded access policy should be made publicly available with reference to the products to which the policy applies.

If a pharmaceutical company or the drug manufacturer that is developing the drug for marketing makes its expanded access policy publicly available and mentions specific drugs for which expanded access is available and provides a link to the relevant information on ClinicalTrials.gov to comply with the requirements of the Cures Act, FDA does not intend to consider this to be

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[40] See 21 U.S.C. 360bbb-0(a) and (b).

[41] See 21 U.S.C. 360bbb-0(c).

[42] A reference to the record in ClinicalTrials.gov may not be available if the trial is not required to be registered at ClinicalTrials.gov. In addition, if the party responsible for registering that clinical trial is not *both* the sponsor of the applicable trial and the manufacturer of the investigational drug product being studied, that responsible party is not required to submit information on the availability of its investigational drug product for expanded access. For further information, refer to the "Frequently Asked Questions" section on the ClinicalTrials.gov website (https://clinicaltrials.gov/ct2/manage-recs/faq).

[43] See 21 U.S.C. 360bbb-0(b).

promotion of an investigational drug or evidence of a new intended use unless the posted policy represents in a promotional context that the investigational new drug is safe or effective for a use for which it is under investigation.[44]

Q37. When is the manufacturer or distributor required to make its expanded access policy publicly available?

FDARA amended section 561A(f) of the FD&C Act[45] to require that the manufacturer or distributor of investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions make the expanded access policy public and readily available by the earlier of the following dates:

- At the first initiation of a phase 2 or phase 3 study[46]
- Fifteen days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy[47]

FDA recommends that the pharmaceutical company or the drug manufacturer that is developing the drug for marketing, rather than the distributor, make its expanded access policy publicly available. FDA interprets "initiation of a phase 2 or phase 3 study" to be when enrollment begins. At the initiation of the phase 2 or 3 trial, it is the responsibility of the pharmaceutical company or the drug manufacturer that is developing the drug for marketing to identify whether the investigational drug is intended to treat a serious disease or condition and to make the expanded access policy public and readily available to comply with the requirement. An FDA designation of fast track, breakthrough therapy, or regenerative advanced therapy indicates that the drug is intended to treat a serious disease or condition. The requirement of making expanded access policies public and readily available by the specified timelines does not preclude posting the policies at an earlier point in time.

Q38. Where can patients and health care providers get information about the availability of drugs under expanded access?

Information about the availability of expanded access to an investigational drug may be found on the website of the relevant pharmaceutical company, drug manufacturer, or distributor. The information may also be found on other publicly available websites. The Reagan-Udall Foundation's[48] Expanded Access Navigator website (https://navigator.reaganudall.org/expanded-

[44] See 21 CFR 201.128 and 21 CFR 312.7(a).

[45] See 21 U.S.C. 360bbb-0(f).

[46] See 21 U.S.C. 360bbb-0(f)(1); see also 21 CFR 312.21(b) and (c).

[47] See 21 U.S.C. 360bbb-0(f)(2).

[48] The Reagan-Udall Foundation for the Food and Drug Administration is an independent 501(c)(3) organization created by Congress "to advance the mission of the FDA to modernize medical, veterinary, food, food ingredient,

access-navigator) has a Company Directory web page (https://navigator.reaganudall.org/company-directory) that includes (1) a list of pharmaceutical companies and drug manufacturers developing investigational drugs for marketing and (2) information about the availability of their drugs under expanded access (e.g., hyperlinks to the company's own publicly available website describing its expanded access policy, contact information, and information on the expected time frame for acknowledgement of such requests).

Information about the availability of investigational drugs under expanded access may also be available at ClinicalTrials.gov under certain circumstances. If the party responsible for registering that trial is both the sponsor of the trial and the manufacturer of the investigational drug product being studied, that responsible party is also required to submit to ClinicalTrials.gov certain information on the availability of its investigational product for expanded access, including the type of expanded access being offered.[49] This information on expanded access is then included on the ClinicalTrials.gov website. However, not all clinical trials must be registered on ClinicalTrials.gov. If information about expanded access availability for a particular investigational drug is not included on ClinicalTrials.gov, physicians or patients may wish to contact the sponsor (or manufacturer of the investigational drug, if different from the sponsor) about possible availability.

and cosmetic product development, accelerate innovation, and enhance product safety." See https://reaganudall.org/about-us.

[49] See 42 CFR 11.28(a)(2)(ii)(H) and 11.28(c). In general, a sponsor-investigator of a single patient IND who obtains a letter of authorization from another sponsor to cross-reference manufacturing information would not be considered responsible for submitting information on the availability of the product for expanded access on ClinicalTrials.gov because the sponsor-investigator is not the manufacturer of the investigational product.

APPENDIX A: TABLE OF FDA EXPANDED ACCESS SUBMISSION SUB-CATEGORIES[1]

Subcategory	Waiting Period Before Treatment May Begin	IRB Requirements	Key Distinctions
Individual Patient Expanded Access IND - *Non-Emergency Use*	30 days from FDA receipt date (unless FDA authorizes earlier)	IRB review and approval required before treatment	• New IND submission • Single patient use
Individual Patient Expanded Access Protocol - *Non-Emergency Use*	No waiting period after the protocol is submitted to FDA (treatment may begin immediately)	IRB review and approval required before treatment	• Protocol submitted to existing active IND • Single patient use
Individual Patient Expanded Access IND - *Emergency Use*	Treatment may start immediately upon FDA authorization	Emergency use must be reported to IRB within 5 working days of emergency use	• For acute medical emergencies only • New IND submission • Single patient use • Initial authorization by telephone; written IND due to FDA within 15 working days of authorization
Individual Patient Expanded Access Protocol - *Emergency Use*	Treatment may start immediately upon FDA authorization	Emergency use must be reported to IRB within 5 working days of emergency use	• For acute medical emergencies only • Protocol submitted to existing active IND • Single patient use • Initial authorization by telephone; written protocol due within 15 working days of authorization
Intermediate-Size Patient Population IND	30 days from FDA receipt date (unless FDA authorizes earlier)	IRB review and approval required before treatment	• New IND submission • Multiple patients (typically fewer than a treatment IND/protocol) • Requires evidence of safety for clinical trial at the proposed dose and duration in the approximate number of patients expected to receive the drug under expanded access • Requires preliminary clinical evidence of effectiveness
Intermediate-Size Patient Population Protocol	No waiting period after the protocol is submitted to FDA (treatment may begin immediately)	IRB review and approval required before treatment begins	• Protocol submitted to existing active IND • Multiple patients (typically fewer than a treatment IND/protocol) • Same evidence requirements as intermediate IND
Treatment IND	30 days from FDA receipt date (unless FDA authorizes earlier)	IRB review and approval required before treatment	• New IND submission • Large/widespread population • For the expanded access use, the drug must be in controlled clinical trial under an

[1] For detailed information about the requirements for the subcategories, see Q6 and Q9.

Subcategory	Waiting Period Before Treatment May Begin	IRB Requirements	Key Distinctions
			IND supporting a marketing application or sponsor actively pursuing marketing approval following trial completion • When for serious disease or condition, sufficient clinical evidence of safety and effectiveness; when for immediately life-threatening disease or condition, available scientific evidence provides reasonable basis to conclude that drug may be effective for expanded access use and would not expose patients to unreasonable and significant risk of illness or injury
Treatment Protocol	30 days from FDA receipt date (unless FDA authorizes earlier)	IRB review and approval required before treatment	• Protocol to existing active IND • Large/widespread population • Unique among protocols - has 30-day waiting period • Same clinical trial/marketing/evidence requirements as treatment IND

APPENDIX B: INFORMED CONSENT TEMPLATE FOR INDIVIDUAL PATIENT EXPANDED ACCESS[2]

Disclaimer: The purpose of this informed consent template is to assist investigators with preparing an informed consent document for the treatment of a single patient with an investigational drug under the expanded access program. Physicians and institutions may use this template to model their forms for obtaining informed consent from patients. However, this template is not a substitute for the Federal Food, Drug, and Cosmetic Act (FD&C Act) or the Code of Federal Regulations (CFR) and does not necessarily contain all information required to ensure compliance in a given situation. Investigators are responsible for ensuring that the informed consent requirements of 21 CFR part 50 are met (see 21 CFR 312.305(c)(4)) unless one of the exceptions found in part 50 applies.

1. Introduction

Provide the following information:

- *The name of the disease or condition for which the investigational drug/biological product will be provided for treatment.*
- *A statement that the patient does not have any alternative Food and Drug Administration (FDA)-approved medical product (e.g., drug/biological product) available to them for treatment.*
- *The name of the investigational drug/biological product.*
- *An explanation that the product is investigational, is not approved by FDA as safe and effective, and that the treatment is an experimental treatment. A statement that the treatment may only proceed under FDA's expanded access program, with FDA authorization.*[3]
- *A statement that the patient's participation in the program is voluntary and that the patient may change their decision to participate. Provide the name of the person the patient may contact in case the patient changes their decision.*
- *A statement that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.*
- *A recommendation to read the form carefully and discuss with others (e.g., patient's doctor, clinical staff, family, friends) before making any decision.*

[2] This template consists of instructions (*in italics*) to create the template and includes some example language (below the instructions) for each element. Once the template is finalized, delete the instructions from the template.

[3] See Q14 of the guidance.

- *The name of the doctor or clinical staff whom the patient can contact if the patient has questions.*

Examples:[4]

- You are diagnosed with disease X.

- For your condition, there is no drug approved by the Food and Drug Administration (FDA) for use in routine medical care in the United States. **OR** The Food and Drug Administration (FDA)-approved drug or drugs available for your treatment did not work for you. **OR** You cannot tolerate the side effects of the drug or drugs approved by the Food and Drug Administration (FDA) for treatment of your condition.

- Your doctor would like to treat you with drug Y.

- Drug Y is an investigational drug. It is *NOT* approved by FDA for the treatment of your disease. However, for your case, FDA authorized Dr. Z to treat you with the investigational drug Y under FDA's expanded access program, **OR** Dr. Z has requested or will request FDA's permission to treat you with the investigational drug Y under FDA's expanded access program.

- Whether or not you take this investigational drug is up to you. If you choose not to receive the investigational drug, it will not result in penalty or loss of benefits to which you are otherwise entitled.

- You can choose to take the investigational drug now but change your mind later. Tell your doctor right away about your decision if you change your mind later. It will not result in any penalty or loss of benefits to which you are otherwise entitled.

- Read this document carefully. You may want to discuss your options with your doctors, family, friends, and others before deciding on whether to receive the treatment. Please ask questions about anything you do not understand. You will find a contact information table at the end of this document.

2. What are the potential benefits of receiving the treatment?

List the potential benefits of the investigational drug/biological product, if any. Include a statement to reflect that the anticipated benefit may be uncertain or that the disease may worsen with the treatment.

Examples:

[4] In the examples in this appendix, *drug* is used as a reference. In your document, use *drug* or *biological product*, as appropriate.

- There is a chance that the investigational drug Y may (1) improve . . ., (2) reduce . . ., etc. However, there is no guarantee that it will happen in your case.

- Dr. Z would like to treat you with the investigational drug because she believes that it may benefit you. However, there is no guarantee that you will benefit from this investigational treatment. It is possible that you will receive no benefit other than receiving the standard care (regularly seen by a doctor, evaluated for your condition, etc.) associated with receiving this treatment, or it could worsen your condition.

- We do not know if this investigational drug will help you. Your condition may get better, stay the same, or possibly get worse.

3. What are the potential risks of this treatment?

Provide a list of reasonably foreseeable risks or side effects of the investigational drug/biological product. Include frequency, if known. Include information on risks that are more likely to occur and those that are serious. Discuss any potential risks from the medical procedures necessary to administer the drug/biological product, if appropriate. Provide specific instructions for whom the patient should contact if experiencing serious side effects.

Examples:

- There is a risk that the investigational drug Y makes your condition worse.

- The following are serious side effects that have been reported for the investigational drug Y:

  - Serious injury to your kidneys that could lead to dialysis
  - Significant disability

- The following are side effects that are more likely to occur:

  - Vomiting
  - Diarrhea
  - Lack of appetite

- The investigational drug needs to be administered via [W] route of administration during [X procedure]. Risks of [X procedure] may include headache, pain or numbness in the legs and lower back, and bleeding into the spinal canal where the main nerve that goes down your back is located. The doctors who will perform the [X procedure] are specifically trained and experienced in performing this procedure.

- There may be side effects of the investigational drug Y that we do not know about.

  - These effects could be immediate and short term, or your future health may be affected in ways that we currently do not understand.

- If you experience side effects listed above or any other adverse effects, contact the staff listed in the contact information table.

- In case of emergency, contact the staff listed in the contact information table or get emergency medical help immediately.

4. How long will you be treated with the investigational drug/biological product?

Describe the length of time the treatment will last (e.g., hours, days, weeks, months, years, or until a certain event), as well as long-term follow-up, if appropriate. Include number of visits or treatments as applicable.

Examples:

- You will receive the investigational drug approximately every 2 months (6–8 weeks) for up to 1 year.

- After you complete this treatment, you will still need to come to the clinic for follow-up visits for at least the next year.

5. If you do not accept this treatment, what are the other choices?

Explain that to provide an investigational drug/biological product under expanded access, the doctor should determine there is no available comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition and that the doctor has made such a determination.

Examples:

- Dr. Z determined that there are no other drugs approved to treat your disease.

- There are no other drugs approved for your disease or clinical trials in which you could enroll. However, you can discuss other options with Dr. Z, such as not taking any investigational drug.

6. What are the procedures associated with the treatment?

Describe in chronological order the procedures that are necessary as part of receiving the treatment. Use a table, if needed, to organize the information. If describing every procedure will make the document too lengthy or detailed, include the information as an addendum.

Examples:

Date (chronological order)/frequency	Description of therapy; dose, route of administration	Duration
Approximately every 2 months (i.e., 6–8 weeks)	Administer drug Y in your vein (10 mg/kg)	90 minutes

Date (chronological order)/frequency	Procedure for assessment	Purpose
Day 1	Collect blood samples	Routine laboratory tests
Month 4	CT scan to take a picture of your X	If there is any change in the size of the tumor

7. Can your doctor stop the treatment without your permission?

Provide a list of reasons for which the doctor may stop the treatment without the patient's consent. Explain that the patient will be notified if this happens.

Examples:

In certain situations, your doctor may need to stop the investigational drug without your permission if:

- Your condition gets worse.
- The investigational drug is no longer safe for you.
- New information suggests that this investigational drug does not work.
- You become pregnant.
- New information suggests that another investigational drug is better.
- FDA tells your doctor that your treatment should be stopped. This may happen if FDA receives new information about the investigational drug that your doctor may not know because it is confidential.
- The investigational drug is no longer available from the manufacturer.

If your doctor stops your treatment, we will tell you as soon as possible.

8. What is the cost of the treatment?

Explain that the patient may incur expenses for the treatment with the investigational drug/biological product. Explain to the best of your knowledge what costs the patient is likely to need to cover and that insurance may not cover all costs. Because the coverage of treatment with an investigational drug/biological product could be complex, it may be appropriate to recommend that the patient consult their insurer about reimbursement before initiating the treatment.

Examples:

- You or your insurance company will be charged for the treatment. You will be responsible for any costs your insurance does not cover. Contact your insurance company if you have any questions about these costs or what out-of-pocket expenses you may have.

- The [INSTITUTION] will pay for the treatment, including treatment of any side effect, illness, or injury to you resulting from the treatment.

- If you receive this treatment, your insurance may not cover the cost of some of the tests and visits to see your doctor that are related to receiving this investigational drug. Contact your insurance company to learn more about the coverage if you decide to receive the treatment.

- Dr. Z's research funds will pay for some items and services related to your treatment. However, you and your insurer will be responsible for the remaining costs. Please contact the person listed in the contact information table to learn more about the coverage by research fund.

- If you need financial assistance to cover the cost of your treatment, please contact the doctor/clinical staff listed in the contact information table for more information.

9. What happens if you are injured from the treatment?

Provide the following information about treatment-related injuries:

Describe any compensation and medical treatments available to the patient if injury occurs.

Provide the names and contact information of the staff whom the patient should contact if further information is needed. The available compensation and medical treatments may vary depending on the medical circumstances of the patient or the policies of the institution.

Examples:

- If this treatment results in an injury, [INSTITUTION] will provide you with medical care.

- Cost for care related to treatment-related injuries will be billed in the ordinary manner to you or your insurance company.

10. Who may see, use, or share your health information?

Provide information about the confidentiality policy of the clinic/hospital/sponsor OR include the list of your policies. Include a statement that the data from this investigational treatment will be shared with FDA and note the possibility that FDA may inspect the records related to the investigational treatment.

Examples:

- If you receive this investigational drug, certain information about your treatment may be shared with the following entities, but every effort will be made to keep your identity private:
  - The manufacturer of the drug
  - The Food and Drug Administration
  - The institutional review board
- In addition, the following people/institutions may have access to your identity and information about your use of the investigational drug:
  - Your insurance company or health benefits program
  - The clinic staff directly involved in your medical care
- If you stop treatment, information that was already collected may still be shared with FDA.
- If the result of this treatment is published, your personal identifying information will not be used.
- Although it is unlikely to happen, there is a possibility that your personal information will be disclosed accidentally.

11. What other important information do you need to know?

Provide a list of other important information not covered in the sections above.

Examples:

- During your treatment, if we learn any new information about the risks or benefits of the investigational drug Y, Dr. Z will let you know.
- You will not receive any payment as compensation to take the investigational drug Y.
- You may review our web-based interactive educational program for patients with your disease at the following link: [insert URL link].

Whom should I contact?

Provide consolidated contact information, as appropriate. If the contact information changes at any time, provide the new contact information to the patient.

Examples:

Name **(Name of the doctor/clinical staff/board/IRB/advocate, etc.)**	**Contact information** **(Phone number, email, or address, etc., as appropriate)**	**For questions about…** **(Provide a consolidated list of issues for which a patient may have questions)**
Name of the doctor/clinical staff	Phone: E-mail: Address:	• Treatment, including any injury from the treatment • Emergency contact information, including 24-hour contact information, if appropriate
Name of the doctor/clinical staff/board/IRB/advocate	Phone: E-mail: Address:	• Administrative concerns (e.g., patient rights, billing)

12. Permission Signatures

Include the list of signatories who should provide consent for the treatment. Provide instructions for the assent process if you have any specific policies.[5]

Examples:

Your signature below provides your consent to take part in this investigational treatment.

_____

Name of patient

[5] For FDA's recommendations on the assent process for children, see the draft guidance for industry, sponsors, and IRBs *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022). When final, this guidance will represent FDA's current thinking on this topic. 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.

Signature of patient	Date Time
Name of legally authorized representative (if needed)	
Signature of legally authorized representative (if needed)	Date Time
Legally authorized representative's relationship to patient (if needed)	

Add any other signatures (e.g., person obtaining consent), following your institutional policy.

1