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**Institutional Review Board (IRB)
Review of Individual Patient Expanded
Access Requests for Investigational
Drugs and Biological Products During
the COVID-19 Public Health
Emergency**

**Guidance for IRBs and Clinical
Investigators**

June 2020

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

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1414 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and the FDA webpage titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to Clinicaltrialconduct-COVID19@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1414 and complete title of the guidance in the request.

Questions

For questions about this document, contact us via email at Clinicaltrialconduct-COVID19@fda.hhs.gov.

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Institutional Review Board (IRB) Review of Individual Patient Expanded Access Requests for Investigational Drugs and Biological Products During the COVID-19 Public Health Emergency

Guidance for IRBs and Clinical Investigators

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 staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

During the COVID-19 public health emergency, the Agency has received a substantially increased volume of individual patient expanded access requests for COVID-19 investigational drugs.¹ Although FDA has issued guidance on expanded access requests, including expanded access for individual patients,² the Agency is aware that Institutional Review Boards (IRBs) seek clarity

¹ For purposes this guidance, unless otherwise noted, the term drug refers both to a drug approved under section 505(c) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and to biological products licensed under section 351 of the Public Health Service Act (PHS Act) 42 USC 262.

² See, e.g., guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (October 2017), available at <https://www.fda.gov/media/85675/download>; guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (October 2017), available at <https://www.fda.gov/media/91160/download>; and information sheet guidance for sponsors, clinical investigators, and IRBs *Waiver of IRB Requirements for Drug and Biological Product Studies* (October 2017), available at <https://www.fda.gov/media/75152/download>.

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regarding the key factors and procedures IRBs should consider when reviewing individual patient expanded access submissions, including for reviews conducted by a single member of the IRB, to fulfill its obligations under 21 CFR Part 56. Therefore, FDA is issuing this guidance to provide recommendations regarding the key factors and procedures IRBs should consider when reviewing expanded access submissions for individual patient access to investigational drugs for treating COVID-19.

This guidance is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS), including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)). However, the recommendations described in the guidance are expected to assist the Agency more broadly in its continued efforts to facilitate access to drugs through expanded access for individual patients beyond the termination of the COVID-19 public health emergency and reflect the Agency's current thinking on this issue. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

Given this public health emergency relating to COVID-19 declared by HHS, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2," and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.³ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁴

The COVID-19 public health emergency has led to a substantial increase in the number of requests

³ Secretary of Health and Human Services Alex M. Azar II, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁴ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

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

Under FDA regulations, three categories of expanded access investigational new drug applications (INDs) are available: Individual (also known as single) patient INDs, including for emergency use (sometimes called "eINDs"); intermediate-size INDs for intermediate-size patient populations; and "treatment" INDs for larger populations.⁸ This guidance applies to IRB review of individual patient expanded access INDs, as outlined in 21 CFR 312.310.⁹

This guidance does not address IRB review of intermediate-size and treatment expanded access requests, as outlined in 21 CFR 312.315 and 312.320, respectively. In general, IRB review of intermediate-size expanded access requests and treatment expanded access requests do not focus on weighing the potential risks and potential benefits for an individual patient based on their unique clinical characteristics; instead, they require an assessment of the potential risks and potential benefits for a population of patients. Therefore, additional information may be necessary to facilitate IRB review for intermediate-size expanded access requests and treatment expanded access requests, which are not addressed in this guidance.

An individual patient expanded access request can be submitted to FDA by a licensed physician as a new IND or by a sponsor of an existing IND as a protocol amendment.¹⁰ A request for emergency individual patient expanded access does not require prior IRB review, but the IRB must be notified within five working days of treatment initiation, and any subsequent use of the investigational drug is subject to IRB review.¹¹ For non-emergency expanded access requests for individual patients, prior IRB review and approval is required before treatment begins.¹²

A licensed physician who submits a non-emergency individual patient expanded access IND may request a waiver¹³ from the requirement for full IRB review.¹⁴ FDA concludes that such a waiver is

⁵ See 21 CFR 312.310.

⁶ See 21 CFR 312.300 and 312.305.

⁷ See 21 CFR 312.300. See also guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (October 2017), available at <https://www.fda.gov/media/85675/download>.

⁸ See 21 CFR 312.310, 312.315, and 312.320.

⁹ See 21 CFR 312.310.

¹⁰ *Ibid.*

¹¹ See 21 CFR 56.104(c).

¹² See 21 CFR 312.305(c)(4); 21 CFR 56.103.

¹³ See 21 CFR 56.105.

¹⁴ See 21 CFR 56.108(c).

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appropriate for individual patient expanded access INDs when the physician obtains concurrence from the IRB chairperson or another designated IRB member before treatment begins.¹⁵ A waiver from the requirement for full IRB review would also extend to any changes/amendments to the original treatment plan or for continuing review of the individual expanded access IND request.

IRB review of an expanded access request for an individual patient, including review by a single member of the IRB under a waiver request, should focus on the key factors needed to assess the risks and benefits of treatment for the particular patient involved. As discussed above, FDA is aware that IRBs are seeking clarity regarding the key factors and procedures they should consider when reviewing individual patient expanded access requests, including IRB reviews conducted by single members, to fulfill its obligations under 21 CFR Part 56. Below, FDA provides recommendations to IRBs on those key factors and procedures to consider.

III. Recommendations on IRB Procedures and Factors to Consider for Individual Patient Expanded Access Requests

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

FDA recommends that IRBs:

- Consider establishing procedures for a single IRB member to review an expanded access submission for an individual patient if the physician requests a waiver¹⁶ from the requirements for review by the full IRB.¹⁷ These procedures should reflect the information that the IRB deems relevant for a single IRB member review and should include procedures designed to ensure that the member documents the decision to concur or not concur with the treatment.
- Focus the review of an expanded access request for an individual patient on assessing the risks and benefits for the patient involved. The information reviewed by the IRB must be adequate to assess whether risks to the patient have been minimized and that such risks are reasonable in relation to anticipated benefits.¹⁸ FDA regulations under 21 CFR 56.111 outline the criteria for IRB review of research. In the context of an individual patient expanded access request, FDA does not expect that a protocol will be necessary to provide

¹⁵ A physician may request such a waiver by checking Box 10(b) on Form FDA 3926, which is a streamlined alternative to Form FDA 1571. Form FDA 3926 was created specifically for physician-submitted individual patient expanded access INDs, including those for emergency use. A physician submitting an individual patient expanded access IND using Form FDA 1571 may include a separate waiver request with the application. See Question 6 in guidance for industry *Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers* (October 2017), available at <https://www.fda.gov/media/85675/download>.

¹⁶ See 21 CFR 56.105 and footnote 15.

¹⁷ See 21 CFR 56.108(c).

¹⁸ See 21 CFR 56.111(a)(1) and (a)(2).

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the IRB with sufficient information to determine if those criteria are satisfied.¹⁹ A thorough patient history and treatment plan, included in the Form FDA 3926 or in another document, can be sufficient to provide the information necessary for an IRB assessment. Such information should include:

- The proposed daily dose, route, and frequency of administration, duration of planned treatment, criteria for discontinuation of treatment, and planned dose modifications for adverse events;
- The planned monitoring for adverse events, response to treatment, and changes in clinical status, as well as proposed modifications to the treatment plan to mitigate risks to patients if appropriate;
- The key details of the patient’s history, including diagnosis and summary of prior therapy (including response to such therapy), as well as information regarding a patient’s relevant clinical characteristics (such as comorbid conditions and concomitant medications) that are necessary to assess the potential for increased risks of the drug; and
- A summary of known risks of the drug.

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

- Assess the qualifications of the physician submitting the individual patient expanded access request.²⁰
- When the request is for a pediatric patient, confirm that adequate provisions are included for soliciting age-appropriate assent from children and permission from a parent or guardian, as required under 21 CFR 50.55.
- Confirm that the informed consent document contains the information required under 21 C.F.R 50.25. As described above, the primary purpose of expanded access is to use the drug to diagnose, monitor, or treat a patient’s disease or condition rather than to generate scientific information intended to characterize the safety and effectiveness of a drug. 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 COVID-19, to satisfy the requirement under 21 C.F.R §50.25(a)(1) that the informed consent provide a statement that the use of the product “involves research.”

¹⁹ For individual expanded access protocol amendments submitted by sponsors to their existing IND, the IRB is likely to receive a protocol for review.

²⁰ See 21 CFR 56.107(a), 21 CFR 56.111, and FDA’s guidance for IRBs, clinical investigators, and sponsors *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed* (August 2013), available at <https://www.fda.gov/media/85294/download>.