



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-3124]

Adaptive Designs for Clinical Trials of Drugs and Biologics; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics." This guidance provides guidance to sponsors and applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biological product. The guidance describes important principles for designing, conducting, and reporting the results from an adaptive clinical trial. This guidance finalizes the draft guidance entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics" issued in October 2018.

FDA is also announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit either electronic or written comments on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: To ensure that comments on the information collection are received, please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on

or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date. OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the title "Adaptive Designs for Clinical Trials of Drugs and Biologics" and the OMB control number 0910-0014. Also include the FDA docket number found in brackets in the heading of this document.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-D-3124 for "Adaptive Designs for Clinical Trials of Drugs and Biologics." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law.

For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Scott Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-794-2055; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

Regarding the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRASStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a final guidance for industry entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics." The guidance provides recommendations to sponsors and applicants submitting INDs, NDAs, BLAs, or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. Agency regulations in 21 CFR parts 312, 314, and 601 govern the format and content of information that must be included in IND, NDA, and BLA submissions, respectively, and set forth general requirements regarding supporting documentation and recordkeeping associated with the various applicable provisions.

Recommendations found in the guidance describe principles we consider important for designing, conducting, and reporting the results from an adaptive clinical trial. The guidance also discusses the types of information FDA will evaluate from clinical trials with adaptive designs, including Bayesian adaptive and complex trials that rely on computer simulations for their design. The primary focus of this guidance is on adaptive designs for clinical trials intended to support the effectiveness and safety of drugs and biological products.

This guidance finalizes the draft guidance of the same title issued on October 1, 2018 (83 FR 49400). FDA considered comments received on the draft guidance as the guidance was finalized. Changes from the draft to the final guidance include: (1) reworking the subsection on Bayesian adaptive designs to clarify the Agency's recommendations and (2) clarifying the extent of prespecification required for the rules governing adaptations. In addition, editorial changes were made to improve clarity.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Adaptive Designs for Clinical Trials of Drugs and Biologics." 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.

II. Paperwork Reduction Act of 1995

In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Investigational New Drug Regulations

OMB Control Number 0910-0014--Revision

In accordance with 21 CFR 312.145, we are making this guidance available under our good guidance practices regulations in 21 CFR 10.115 to help respondents comply with regulatory requirements associated with submitting INDs, NDAs (currently approved under OMB control number 0910-0001), and BLAs (currently approved under OMB control number 0910-0338). In section VIII.B., the guidance states that the documented plan for a clinical trial with a proposed adaptive design should include certain information. The information could be included in the clinical trial protocol and/or in separate documents, such as: (1) a statistical analysis plan, (2) a data monitoring committee (DMC) charter, or (3) an adaptation committee charter. Although different types of information might be included in different documents, all important information described below should be submitted to FDA during the design stage so that FDA has sufficient time to provide feedback prior to initiation of the clinical trial:

- A rationale for the selected design;

- A detailed description of the monitoring and adaptation plan, including the anticipated number and timing of interim analyses, the specific aspects of the design that may be modified, and the rule that will be used to make adaptation decisions;
- Information on the roles of the bodies responsible for implementing the adaptive design, such as the DMC and/or the dedicated adaptation committee, if applicable;
- Prespecification of the statistical methods that will be used to produce interim results, guide adaptation decisions, carry out hypothesis tests, estimate treatment effects, and estimate uncertainty in treatment effect estimates at the end of the trial;
- Evaluation and discussion of the design operating characteristics; and
- In cases where simulations are the primary or sole technique for evaluating trial operating characteristics, a detailed simulation report should be submitted, including:
 - An overall description of the trial design;
 - Example trials, in which a small number of hypothetical trials are described with different conclusions, such as a positive trial with the original sample size, a trial stopped for futility after the first interim look, a positive trial after increasing the sample size, etc.;
 - A description of the set of parameter configurations used for the simulation scenarios, including a justification of the adequacy of the choices;
 - The number of simulated trials (iterations) evaluated for each scenario and a rationale for the adequacy of this number;
 - Simulation results detailing the estimated operating characteristics under the various scenarios;
 - Simulation code that is readable and adequately commented and should include the random seeds used to generate the simulation results; and
 - A summary providing overall conclusions.

- A comprehensive written data access plan defining how trial integrity will be maintained in the presence of the planned adaptations. This documentation should include information regarding: (1) the personnel who will perform the interim analyses, (2) the personnel who will have access to interim results, (3) how that access will be controlled, (4) how adaptive decisions will be made, and (5) what type of information will be disseminated following adaptive decisions, and to whom it will be disseminated. The data access plan should describe what information (and under what circumstances) is permitted to be passed to the sponsor or investigators. In addition, it is recommended that sponsors establish procedures to evaluate compliance with the data access plan and to document all interim meetings of the committee tasked with making adaptation decisions (i.e., the DMC or other adaptation committee). For example, interim meetings should be documented with written meeting minutes describing what was reviewed, discussed, and decided.

In section VIII.C., the guidance states that a marketing application to FDA that relies on a trial with an adaptive design should include sufficient information and documentation to allow FDA to thoroughly review the results, including:

- All prospective plans, any relevant committee charters (e.g., the DMC or adaptation committee charter), and any supporting documentation (e.g., literature references, programming code, simulation report);
- Information on compliance with the planned adaptation rule and with the procedures outlined in the data access plan to maintain trial integrity;
- Records of deliberations and participants for any interim discussions by any committees involved in the adaptive process;
- Results of the interim analyses or analyses used for the adaptation decisions; and

- Appropriate reporting of the adaptive design and trial results in section 14 of the proposed package insert. For example, the trial summary should describe the adaptive design utilized. In addition, treatment effect estimates should adequately take the design into account, or if naïve estimates such as unadjusted sample means are used, the extent of bias should be evaluated, and estimates should be presented with appropriate cautions regarding their interpretation.

Discussion of the plans for an adaptive trial can be the basis for requesting a Type C meeting.

Regulatory mechanisms for obtaining formal, substantive feedback from FDA on clinical trials may also include end-of-phase-2 meetings. The guidance also recommends that special protocol assessments (given the 45-day response timeline) be submitted for trials with complex adaptive designs only if there has been extensive previous discussion between FDA and the sponsor regarding the proposed trial and design. The guidance explains that in their submissions, sponsors should prespecify the details of the adaptive design and provide justification that the chances of erroneous conclusions will be adequately controlled, estimation of treatment effects will be sufficiently reliable, and trial integrity will be appropriately maintained. The guidance notes that the sponsor should advise FDA during the course of a trial of any proposed changes to the trial design (usually through protocol amendments) and that FDA may request that the sponsor submit minutes from open sessions of a monitoring committee during an ongoing trial.

As noted above, in the *Federal Register* of October 1, 2018, FDA published a 60-day notice requesting public comment on the proposed collection of information.

There were 21 distinct commenters during this time frame, including from industry, drug associations, individuals, and academia, with multiple comments from each distinct commenter.

The majority of comments on the guidance related to format, clarity, or word choice, providing specific technical recommendations on statistical methodologies. Because we do not believe these

considerations have any effect on the information collection burden, we have made no changes to our estimate.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Clinical trial protocols and related submissions to FDA with an adaptive design and analysis plan should contain the information in section VIII.B.	40	6	240	50	12,000
Marketing applications that rely on studies with an adaptive design should contain the information in section VIII.C.	15	1.33	20	50	1,000
Total					13,000

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Based on our review of INDs, NDAs, BLAs, and supplemental applications for the use of adaptive designs for clinical trials to provide evidence of effectiveness and safety, we estimate that approximately 40 sponsors or applicants will prepare approximately 240 documented plans for clinical trials containing a proposed adaptive design and analysis plan and will submit this information to FDA in a clinical trial protocol and/or in separate documents such as a statistical analysis plan, a data monitoring committee charter, or an adaptation committee charter. In addition, we estimate that preparing and submitting this information will take approximately 50 hours per sponsor or applicant.

Furthermore, we estimate that approximately 15 sponsors or applicants will prepare and submit to FDA approximately 20 marketing applications that rely on a trial with an adaptive design and that preparing and submitting this information will take approximately 50 hours per sponsor or applicant.

FDA is issuing this final guidance subject to OMB approval of the collections of information. Before implementing the information collection provisions of the guidance, FDA will publish a notice in the *Federal Register* announcing OMB's decision to approve, modify, or disapprove the collections of information, including OMB control number(s) for newly approved collections.

III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>, or <https://www.regulations.gov>.

Dated: November 25, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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