(b) The records required by this regulation shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

* * * * *

■ 19. In § 56.121, revise the last sentence in paragraph (c) to read as follows:

§ 56.121 Disqualification of an IRB or an institution.

* * * * *

(c) * * * In addition, the Agency may elect to publish a notice of its action.

* * * * *

■ 20. Revise § 56.122 to read as follows:

§ 56.122 Public disclosure of information regarding disqualification.

A determination that FDA has disqualified an IRB or an institution and the administrative record regarding that determination are disclosable to the public under part 20 of this chapter.

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

■ 21. The authority citation for part 812 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 360hh–360pp, 360rr–360ss, 360bbb–8b, 371, 372, 374, 379e, 381, 382; 42 U.S.C. 216, 241, 262.

■ 22. In § 812.150, revise paragraphs (a)(3) and (b)(5) to read as follows:

§ 812.150 Reports.

(a) * * *

(3) *Progress.* An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly. Such progress reports shall be submitted to the reviewing IRB to the extent that continuing review is required by part 56 of this chapter.

* * * * *

(b) * * *

(5) *Progress reports.* At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRBs. Such progress reports shall be submitted to reviewing IRBs to the extent that continuing review is required by part 56 of this chapter. In the case of a significant risk device, a sponsor shall submit progress reports to FDA at regular intervals, and at least yearly. A sponsor of a treatment IDE shall submit semiannual progress reports to all reviewing IRBs and FDA in accordance with § 812.36(f) and annual progress reports in accordance with this section.

* * * * *

Dated: September 23, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2022–21088 Filed 9–27–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 56

[Docket No. FDA–2019–N–2175]

RIN 0910–AI08

Institutional Review Boards; Cooperative Research

AGENCY: Food and Drug Administration, Health and Human Services (HHS).

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or we) is proposing to replace current requirements for FDA-regulated cooperative research with new requirements that would require any institution located in the United States participating in FDA-regulated cooperative research to rely on review and approval by a single institutional review board (IRB) for that portion of the research that is conducted in the United States, with some exceptions. FDA is also proposing an IRB recordkeeping requirement for research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution. FDA is proposing these revisions to streamline the IRB review process and decrease administrative burdens and inefficiencies for investigators and IRBs without compromising human subject protections. This proposed rule would harmonize FDA's requirements for cooperative research and IRB records, to the extent practicable and consistent with statutory provisions, with the ''Federal Policy for the Protection of Human Subjects'' (revised Common Rule) and is being issued in accordance with a provision of the 21st Century Cures Act (Cures Act).

DATES: Either electronic or written comments on the proposed rule must be submitted by November 28, 2022. Submit written comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 (PRA) by October 28, 2022.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 28, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

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–2019–N–2175 for ''Institutional Review Boards; Cooperative Research.'' Received comments, those filed in a timely manner (see **ADDRESSES**), 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, 240–402–7500.

• 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.'' FDA 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.govinfo.gov/content/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, 240–402–7500.

Submit comments on the information collection under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at *https://www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under Review—Open for Public Comments'' or by using the search function. The title of this proposed collection is Institutional Review Boards—21 CFR part 56 (OMB Control Number 0910–0130—Revision).

FOR FURTHER INFORMATION CONTACT:

With regard to the proposed rule: David Markert, Office of Clinical Policy, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301–796–0752, *David.Markert@fda.hhs.gov.*

With regard to 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, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

This proposed rule would harmonize, to the extent practicable and consistent with statutory provisions, FDA's cooperative research requirements with the cooperative research requirements in the revised Common Rule,[1] which requires use of a single IRB review process for multisite research conducted in the United States, with some exceptions. This proposed rule would establish an IRB recordkeeping requirement that would be harmonized, to the extent practicable and consistent with statutory provisions, with the revised Common Rule's IRB recordkeeping requirement for research overseen by an IRB that is not operated by the institution where the study is conducted. FDA believes that, in many situations, mandatory single IRB review for multi-institutional clinical investigations would streamline the review process and increase efficiencies for the oversight of clinical investigations without compromising human subject protections. Increased efficiencies may facilitate faster initiation of clinical investigations supporting the development of new medical products to benefit the public health. FDA also believes that, in many cases, mandatory single IRB review for multi-institutional clinical investigations would decrease administrative burdens created by multiple IRB reviews for institutions, investigators, IRBs, and sponsors. This proposed rule is being issued in accordance with section 3023 of the Cures Act (Pub. L. 114–255).

B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to replace the current requirements under § 56.114 ''Cooperative research'' of part 56 (21 CFR part 56) with new regulatory text that would require any institution located in the United States participating in cooperative research to rely on approval by a single IRB for that portion of the research that is conducted in the United States, with some exceptions. FDA is also proposing an IRB recordkeeping requirement for research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution.

C. Legal Authority

FDA is proposing to issue this rule under sections 403, 406, 409, 412, 413, 503, 505, 510, 513–515, 520, 531–539, 541–542, 701, and 721 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 343, 346, 348, 350a, 350b, 353, 355, 360, 360c–360e, 360j, 360hh–360pp, 360rr–360ss, 371, and 379e) and section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

D. Costs and Benefits

This proposed requirement for single IRB review for FDA-regulated cooperative research as well as harmonizing, to the extent practicable and consistent with statutory provisions, these FDA requirements

[1] For the purpose of this proposed rule, ''revised Common Rule'' refers to the January 19, 2017, final rule (82 FR 7149), which was modified by an interim final rule that delayed the effective date and general compliance date (83 FR 2885, January 22, 2018) and a final rule that delayed the general compliance date, while allowing use of three burden-reducing provisions for certain research during the delay period (83 FR 28497, June 19, 2018). The compliance date for the cooperative research provisions of the revised Common Rule was January 20, 2020.

with the revised Common Rule should reduce the administrative and coordination costs of conducting cooperative research by: (1) reducing duplicative reviews; (2) facilitating an earlier start of cooperative research; and (3) reducing the need to reconcile variability in IRB review decisions for cooperative research conducted with a common protocol. Reducing the costs of conducting cooperative research should reduce the costs of FDA-regulated medical product development and facilitate an earlier start of cooperative research, which could contribute to a faster introduction of those products into commercial use. Over 10 years, the annualized costs range from approximately $30 million to $134 million with a 7 percent discount rate and range from $30 million to $127 million with a 3 percent discount rate. The annualized net cost savings (benefits net of costs) range from $87 million to $882 million with a 7 percent discount rate and range from $87 million to $897 million with a 3 percent discount rate.

II. Background

TABLE OF ABBREVIATIONS/COMMONLY USED ACRONYMS IN THIS DOCUMENT

Abbreviation/acronym	What it means
AI/AN	American Indian or Alaska Native.
Cures Act	21st Century Cures Act.
FDA	Food and Drug Administration.
IRB	Institutional Review Board.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FR	Federal Register.
HHS	Health and Human Services.
IDE	Investigational Device Exemption.
IND	Investigational New Drug Application.
NIH	National Institutes of Health.
OHRP	Office for Human Research Protections.
NSR	Nonsignificant Risk.
PRA	Paperwork Reduction Act of 1995.
OMB	Office of Management and Budget.
PHS Act	Public Health Service Act.
SACHRP	Secretary's Advisory Committee on Human Research Protections.
U.S.C.	United States Code.

FDA is in the process of amending its regulations under 21 CFR parts 50 and 56 on protection of human subjects and IRBs to harmonize with the revised Common Rule, consistent with section 3023 of the Cures Act. This proposed rule only addresses single IRB review for cooperative research and a related IRB recordkeeping requirement. FDA intends to undertake additional rulemaking to harmonize our regulations with the revised Common Rule, to the extent practicable and consistent with statutory provisions.

A. Single IRB Review Requirements Under the Revised Common Rule

The Common Rule was originally issued in 1991 (56 FR 28001, June 18, 1991). The Common Rule sets forth requirements for the protection of human subjects involved in research that is conducted or supported by the Department of Health and Human Services (HHS) (see 45 CFR part 46, subpart A) and other Federal Departments and Agencies. The purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections as well as to create a uniform body of regulations across the Federal Departments and Agencies (80 FR 53931 at 53935, September 8, 2015).

On January 19, 2017, HHS and the other Common Rule Departments and Agencies announced revisions to modernize, strengthen, and make the Common Rule more effective (82 FR 7149, January 19, 2017). The revised Common Rule is intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators (82 FR 7149). One of the proposals adopted in the revised Common Rule is the requirement for institutions located in the United States that are engaged in cooperative research (also referred to as multi-institutional studies, multisite studies, or multicenter studies) to use single IRB review for that portion of the research that takes place within the United States, with certain exceptions.[2]

In adopting a single IRB review requirement as part of the revised Common Rule, HHS and the other Common Rule Departments and Agencies agreed with those commenters on the proposed rule to revise the Common Rule who indicated that mandated single IRB review would ultimately decrease administrative burdens and inefficiencies for investigators and institutions without diminishing human subject protections, while also acknowledging that transition to the single IRB review model would require additional time and changes to institutional policies and structures. In addition, HHS and the other Common Rule Departments and Agencies stated in the preamble that ''in many cases multiple IRB approvals increase burden and frequently delay the implementation of studies, increasing the costs of clinical trials and potentially stalling access to new therapies.'' (82 FR 7149 at 7209.)

The revised Common Rule requires that all U.S. institutions engaged in cooperative research rely upon a single IRB review with two exceptions: (1) cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native (AI/AN) tribe) or (2) research for which any Federal Department or Agency supporting or conducting the research determines and documents that the use of single IRB review is not appropriate for the particular context (45 CFR 46.114(b)). Under the first exception, if applicable law (including when the official governing body of an AI/AN tribe passes a tribal law) requires more than single IRB review for certain cooperative research, then the revised Common Rule's requirement for single IRB review

[2] For the purpose of this proposed rule, the terms ''central IRB'', ''single central IRB'', ''single IRB'' and ''single IRB of record'' are synonymous and interchangeable. The terms ''site'' and ''institution'' are also intended to be synonymous and interchangeable.

does not apply to such cooperative research (82 FR 7149 at 7209). In addition, the revised Common Rule allows a Federal Department or Agency supporting or conducting the research the flexibility to determine that use of a single IRB is not appropriate for certain contexts, thereby permitting additional IRB review in some circumstances (82 FR 7149 at 7209). While the revised Common Rule does not prohibit an institution from conducting its own additional internal review, ''such reviews would no longer have any regulatory status in terms of compliance with the Common Rule.'' (82 FR 7149 at 7209). For cooperative research subject to this single IRB review mandate, the reviewing IRB will be identified by the Federal Department or Agency supporting or conducting the research, or proposed by the lead institution subject to the acceptance of the Federal Department or Agency supporting the research (82 FR 7149 at 7209).

B. The National Institutes of Health (NIH) Single IRB Policy

On December 3, 2014, the NIH proposed a Draft NIH Policy, ''Use of a Single Institutional Review Board of Record for Multisite Research,'' which stated that NIH would generally expect all domestic sites of multisite NIH-funded studies to use a single IRB of record.[3] In finalizing its policy, NIH explained that, in general, public comments on the Draft NIH Policy were supportive of NIH's goal of enhancing and streamlining IRB review in multisite research. However, NIH also described that some commenters, mainly academic institutions and organizations representing them, expressed concerns about the scope of the proposed policy, did not agree that it should become a term and condition of funding, and pointed to the importance of local IRB review. On the other hand, many NIH stakeholders agreed that the use of single IRB review for multisite studies involving a single protocol would help streamline IRB review and could help enhance protections for human subjects (81 FR 40325 at 40326, June 21, 2016). On June 21, 2016, NIH finalized its policy on the use of single IRB review, which is complementary to the revised Common Rule's cooperative research provision (81 FR 40325 at 40326). NIH's final single IRB policy went into effect on January 25, 2018.[4]

C. The Cures Act

On December 13, 2016, the Cures Act was signed into law amending certain provisions of the FD&C Act. The Cures Act is designed to help accelerate the discovery, development, and delivery of 21st century cures. Section 3023 of the Cures Act directs the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, to harmonize differences between the HHS Human Subject Regulations and FDA's Human Subject Regulations. Section 3023 requires modifications to the HHS and FDA Human Subject Regulations, as appropriate, to: (1) reduce regulatory duplication and unnecessary delays; (2) modernize such provisions in the context of multisite and cooperative research projects; and (3) protect vulnerable populations, incorporate local considerations, and support community engagement through mechanisms such as consultation with local researchers and human research protection programs. The Cures Act also requires the Secretary, as appropriate, to ensure that human subject research that is subject to the HHS Human Subject Regulations and to the FDA Human Subject Regulations may: (1) use joint or shared review; (2) rely upon the review of an independent IRB or an IRB of an entity other than the sponsor of the research; or (3) use similar arrangements to avoid duplication of effort (section 3023 of the Cures Act). FDA is working with the Office for Human Research Protections (OHRP) and others in HHS to carry out this statutory mandate.

In addition, section 3056 of the Cures Act amended section 520(g) of the FD&C Act to remove the requirement for IRBs overseeing clinical investigations of devices to be ''local.'' [5] Before this statutory change, section 520(g) of the FD&C Act required review by a local institutional review committee (*i.e.,* IRB) for clinical testing of a medical device, so requiring single IRB review for clinical investigations of devices was not possible. However, in light of this statutory change, medical device studies may now rely on a single IRB review process.

D. FDA's Current Regulatory Framework

FDA has historically supported efforts to reduce administrative burden in cooperative research. Since being issued in 1981, the IRB regulations at part 56 have provided for the voluntary use of cooperative review in multi-institutional studies (46 FR 8958, January 27, 1981). Under current FDA regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of effort.[6] When FDA's rule, ''Protection of Human Subjects, Standards for Institutional Review Boards for Clinical Investigations'' was proposed, we indicated that the purpose of the section regarding cooperative research was ''to explicitly reduce duplicative review of multi-institutional studies'' (44 FR 47699 at 47700, August 14, 1979). In the preamble to the final rule issuing FDA's regulations at part 56, FDA also stated that ''the purpose of this section is to assure IRBs that FDA will accept reasonable methods of joint review'' (46 FR 8958 at 8970). Additionally, FDA issued guidance in 2006 intended to assist sponsors, institutions, IRBs, and clinical investigators involved in multicenter clinical studies in meeting the requirements of part 56 by facilitating the use of a centralized IRB review process, especially in situations where centralized review could improve efficiency of IRB review.[7] The guidance encourages the use of a centralized IRB review process and provides recommendations regarding how to document agreements and procedures relating to a centralized IRB review system, including those reviews of studies at clinical trial sites not affiliated with the IRB. The guidance also provides some examples of cooperative IRB review models.

E. Need for this Regulation

Although the use of a single IRB review process is already encouraged and consistent with our regulations at § 56.114, it is voluntary. Consistent with the purpose for including the single IRB review requirement for cooperative research in the revised Common Rule, as described above, FDA believes that requiring single IRB review for certain multi-institutional clinical investigations would streamline the review process without compromising human subject protections. In addition, as described in section II.A., FDA believes that the benefits of requiring

[3] *https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html.* On January 6, 2015, NIH published a notice to inform readers of the **Federal Register** about the draft policy and provide an opportunity for comment (80 FR 511).

[4] NOT–OD–17–076 ''Revision: Notice of Extension of Effective Date for Final NIH Policy on Single Institutional Review Board for Multi-Site Research,'' June 16, 2017, *https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-076.html.*

[5] On June 7, 2017, FDA amended its regulations to reflect this statutory change (82 FR 26348).

[6] 21 CFR 56.114.

[7] See FDA's ''Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials'' (March 2006). Available at: *https://www.fda.gov/media/75329/download.*

single IRB review recognized by HHS and the other Common Rule Departments and Agencies would also be realized for multisite, FDA-regulated research, with some exceptions.

Institutions have been reluctant to voluntarily use single IRB review for a variety of reasons, most of which are unrelated to whether single IRB review is more efficient and less burdensome than multiple local IRB reviews. A study conducted by the Clinical Trials Transformation Initiative (CTTI)[8] identified several perceived barriers to the use of single IRB review, including concerns about potential noncompliance by the single IRB, potential loss of local context, and the quality of the single IRB's review. The study found that the perceived barriers to single IRB review resulted from a conflation of institutional responsibilities with the ethical review responsibilities of the IRB, among other factors (Ref. 1).

Over the years, clinical investigations have become more complex, with increasing numbers of sites. For scientific reasons, multicenter clinical investigations generally share a common protocol that could be carried out at each site, or different aspects of the protocol (*e.g.,* study recruitment, data coordination) could be conducted at different sites. In either case, site-specific, local IRB reviews of such a protocol would not be likely to provide additional human subject protections beyond those provided by a single IRB with appropriate expertise to evaluate the risks and benefits of the study, the adequacy of the informed consent process and document, and local issues. In these cases, review by multiple IRBs may lead to unnecessary additional reviews that could delay research without providing an increase in human subject protections. For example, when multiple IRBs are involved in reviewing a cooperative research protocol, a change to the protocol or informed consent document required by one site's IRB could mean that the protocol or informed consent document would need to be resubmitted for review to all the other sites participating in this multisite study, resulting in significant delays in initiating the study. In addition, multiple IRB reviews could result in recruitment differences between sites, leading to difficulty recruiting subjects with the condition of interest, and in some cases, an impact on the generalizability of the study results. Furthermore, multisite clinical investigations can generate large volumes of safety reports; however, duplicative local IRB review of safety reports at every study site may not improve subject safety. A single IRB may be better positioned to review, analyze, and act upon important safety findings.

Examples of administrative burdens and review inefficiencies that result from multiple IRB reviews as described above have also been cited in literature. For example, Greene and Geiger identified numerous related but distinct factors that contribute to research delays and unnecessary costs in multicenter studies that undergo review by multiple IRBs, including: added time for the initial review and approval of the clinical investigation; differing requirements across IRBs that included widely variable IRB approval processes and unique consent forms across sites even in a ''standardized'' environment; differing test subject recruitment procedures and participant incentives across sites, possibly affecting response rates; and, when additional review times and IRB requirements were involved, the additional approval requirements consumed significant amounts of fixed grant funds, reducing the scope of the research (Ref. 2). Several other empirical studies have also found inefficiencies and inconsistencies associated with multiple IRB reviews of multisite clinical investigations (Ref. 3).

In the preamble to the revised Common Rule, the Common Rule Departments and Agencies stated that they believed that merely encouraging single IRB review would ''fail to yield substantive positive change in the system[,]'' and, therefore, determined that requiring single IRB review was necessary in order to increase efficiencies in research (82 FR 7149 at 7209). FDA agrees with the Common Rule Departments and Agencies that the benefits of single IRB review—including a streamlined review process, reduced administrative burdens, and increased efficiencies—are unlikely to be realized if reliance on a single IRB for review of cooperative research remains purely voluntary. Therefore, FDA is proposing to require single IRB review for certain multi-institutional clinical investigations to streamline the review process, decrease administrative burden created by multiple IRB reviews, and reduce inefficiencies for investigators, sponsors, institutions, and IRBs. Increased efficiencies for the oversight of clinical investigations may facilitate faster initiation of clinical investigations for the development of new medical products to benefit the public health. For example, a study of the National Cancer Institute's (NCI) single IRB (Central Institutional Review Board or CIRB) found that the time required to reopen a trial after a temporary closure because of a major protocol amendment was significantly faster at CIRB-affiliated sites (less than 48 hours on average) than at sites that used their local IRBs to implement the same trial amendments (40.5 days on average) (Ref. 4).

Furthermore, a single IRB would provide FDA with a single focal point for an IRB inspection for a given investigation. Inspection of a single IRB could cover oversight of a larger number of clinical investigation sites during a single inspection, therefore providing FDA an opportunity to operate a more efficient IRB inspection program.

FDA recognizes, however, that there are likely to be some initial burdens associated with use of a single IRB, rather than a local IRB model, such as establishing reliance agreements to document responsibilities among the various institutions participating in the research and the reviewing IRB. While FDA agrees with the Common Rule Departments and Agencies that mandatory single IRB review will ultimately decrease administrative burdens and inefficiencies for much FDA-regulated research, for some types of research, we do not believe it is clear that the potential benefits of single IRB review outweigh the potential associated burdens in every circumstance. Therefore, as described below, we are proposing exceptions to the single IRB review requirement to account for these situations.

We note that the preamble to the revised Common Rule describes that some comments identified the importance of local IRB review as a reason for opposing the proposed requirement for use of single IRB review (82 FR 7149 at 7208). FDA believes that attention to local issues related to the communities where the research will take place is very important and has provided recommendations in an FDA guidance on addressing local aspects of IRB review when using a single IRB review process.[9] In general, mechanisms other than a separate local IRB review and approval can be used to address local contextual issues, such as the local site providing the single IRB of record with information on local context and

[8] The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership that focuses on developing and driving adoption of practices that will increase the quality and efficiency of clinical trials (*https://www.ctti-clinicaltrials.org/who-we-are*).

[9] See FDA's ''Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials'' (March 2006). Available at: *https://www.fda.gov/media/75329/download.*

updates, when appropriate. However, because there may be some instances for which local IRB review may be required by law or necessary to provide important expertise for a particular FDA-regulated clinical investigation, FDA is also proposing under § 56.114(b)(2), certain exceptions from the proposed requirement for use of single IRB review to account for those instances.

FDA notes that a substantial amount of the clinical research that FDA regulates is not subject to the revised Common Rule. Although the Common Rule Departments and Agencies conduct and support a significant number of multi-institutional clinical investigations involving FDA-regulated products, the majority of such investigations are conducted and supported by industry. FDA-regulated clinical investigations that are funded by a Common Rule Department or Agency would also be subject to the revised Common Rule, which requires single IRB review for cooperative research, with certain exceptions. Because FDA's proposed mandatory single IRB review provisions would harmonize with the corresponding requirements under the revised Common Rule, to the extent practicable and consistent with statutory provisions, FDA's proposal would reduce the need for sponsors, investigators, institutions, and IRBs to comply with differing requirements. Many institutions are already implementing the revised Common Rule's single IRB review requirement, which had a compliance date of January 20, 2020. In addition, clinical investigations funded by NIH are already subject to NIH's single IRB review policy. Thus, there should be minimal impact on sponsors of FDA-regulated clinical investigations that are also Federally funded.

III. Legal Authority

FDA is proposing to issue this rule under our authority to issue regulations regarding the investigational use of drugs under section 505(i) of the FD&C Act, the investigational use of devices under section 520(g) of the FD&C Act, and the investigational use of biological products under section 351(a) of the PHS Act. In addition, IRB review helps assure the quality and integrity of data from clinical investigations relied upon in submissions to FDA regarding the safety, effectiveness, and/or marketing of FDA-regulated products, including submissions made pursuant to sections 403, 406, 409, 412, 413, 503, 505, 510, 513–515, 520, 531–539, 541–542, and 721 of the FD&C Act and section 351 of the PHS Act. IRB review also helps protect the rights and safety of human subjects involved in those clinical investigations. Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

FDA believes that requiring single IRB review for multi-institutional clinical investigations as described in this proposed rule would streamline the IRB review process, decrease administrative burdens and inefficiencies for investigators and IRBs while maintaining adequate human subject protections, and provide FDA an opportunity to operate a more efficient IRB inspection program.

IV. Description of the Proposed Rule

FDA is proposing to replace the current requirements under § 56.114, Cooperative research, with new regulations that would require any institution located in the United States participating in FDA-regulated cooperative research to rely on approval by a single IRB for that portion of the research that is conducted in the United States, with some exceptions. For research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, FDA is also proposing a new IRB recordkeeping requirement at § 56.115, IRB records. This requirement would clarify the documentation needed to specify the institution's reliance on the IRB for oversight of the research and the responsibilities that the institution, and the organization operating the IRB, will undertake to ensure compliance with the requirements of part 56. These proposed changes address, in part, section 3023 of the Cures Act, which requires the Secretary of HHS to harmonize differences between the HHS Human Subject Regulations and FDA's Human Subject Regulations, to the extent practicable and consistent with other statutory provisions. This proposed rule is intended to fulfill that directive with respect to FDA's requirements for cooperative research and a related IRB recordkeeping requirement. The differences between FDA's proposal and the revised Common Rule are described in further detail below.

A. Single IRB Review Requirement for Cooperative Research

FDA is proposing new regulatory text at § 56.114(a) to describe cooperative research covered by these regulations as a clinical investigation that involves more than one institution and to explain that, in the conduct of cooperative research, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with these regulations. This proposed regulatory text differs from the revised Common Rule at 45 CFR 46.114(a) by using FDA's term ''clinical investigations,'' rather than ''projects,'' and the term ''regulations,'' rather than ''policy.'' This language better reflects the scope of FDA's authority and the terminology used throughout FDA's existing human subject protection regulations.

FDA is proposing new regulatory text at § 56.114(b)(1) to require that any institution located in the United States participating in FDA-regulated cooperative research rely on approval by a single IRB for that portion of the research that is conducted in the United States. This proposed regulatory text differs from the revised Common Rule at 45 CFR 46.114(b)(1) by using FDA's term ''participating,'' rather than ''engaged.'' This language better reflects the terminology used throughout FDA's existing human subject protection regulations.

The revised Common Rule provision at 45 CFR 46.114(b)(1) also requires the reviewing IRB to be identified by the Federal Department or Agency [10] supporting or conducting the research, or to be proposed by the lead institution subject to the acceptance of the Federal Department or Agency supporting the research. It is not practicable for FDA to propose this same requirement because, unlike research subject to the revised Common Rule, most of the research that FDA regulates is not conducted or supported by FDA or by any Federal Department or Agency. FDA's existing regulations do not require that a specific party involved in the research select the IRB when a single IRB process is used, and we are unaware of difficulties in selecting the IRB that warrant requiring the single IRB always to be identified by a particular party for all FDA-regulated research. Because FDA is not proposing to require that a particular party identify the single IRB, there would be no conflict for FDA-regulated research that is also subject to the revised Common Rule requirement that the single IRB be identified by the Federal Department or Agency supporting or conducting the

[10] For purposes of the Common Rule, ''Federal Department or Agency'' ''refers to a federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (*e.g.,* the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).'' 45 CFR 46.102(d).

research or proposed by the lead institution subject to the acceptance of the Federal Department or Agency supporting the research. In addition, FDA's current regulations address the assurance of IRB review for clinical investigations of drugs and devices by an IRB that complies with the regulations set forth in part 56. This assurance is addressed by the responsibilities of sponsors and investigators in an FDA-regulated clinical investigation.[11] In general, for clinical investigations of drugs under 21 CFR part 312, an investigator is responsible for ensuring that there will be initial and continuing review and approval by a qualified IRB (§ 312.66), and a sponsor is responsible for obtaining a commitment from each investigator that he or she will ensure that requirements in part 56 relating to IRB review and approval are met (§ 312.53(c)(1)(vi)(d)). For clinical investigations of medical devices, under part 812 (21 CFR part 812), the sponsor is responsible for ensuring IRB review and approval are obtained (§ 812.40). Additionally, the sponsor is required to identify the reviewing IRB in the investigational new drug (IND) application or an investigational device exemption (IDE) application submitted to FDA.[12]

B. Exceptions to the Single IRB Review Requirement

The revised Common Rule, under 45 CFR 46.114(b)(2), provides two exceptions from the requirement under 45 CFR 46.114(b)(1) for reliance on approval by a single IRB. The following research is excepted: (1) cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an AI/AN tribe) or (2) research for which any Federal Department or Agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context. The preamble to the revised Common Rule noted that the second exception ''allows a federal department or agency the flexibility to determine that the use of a single IRB is not appropriate for certain contexts, thereby permitting additional IRB review and consideration of local and regional variations in some circumstances'' (82 FR 7149 at 7209).

FDA is proposing new regulatory text at § 56.114(b)(2) to provide exceptions to the requirement under § 56.114(b)(1) for reliance on approval by a single IRB. FDA is proposing the same exception as under 45 CFR 46.114(b)(2)(i) of the revised Common Rule for circumstances in which more than a single IRB review is required by law. However, we do not believe it is practicable for FDA to adopt the same regulatory text as the exception at 45 CFR 46.114(b)(2)(ii) because most of the research that FDA regulates is not conducted or supported by FDA or by any Federal Department or Agency. Therefore, this exception would have no applicability to the majority of FDA-regulated research.

We also believe it would be impracticable for FDA to adopt an analogous exception for situations in which FDA determines and documents that the use of a single IRB is not appropriate for the particular context. Unlike review of a research grant application that would be submitted to a Federal Department or Agency for approval, certain FDA-regulated research does not require a submission to FDA or other interaction with FDA before it begins (*e.g.,* research on drugs that is exempt from the requirement to submit an IND application under § 312.2(b) (21 CFR 312.2(b)). If FDA were to require such research to obtain FDA's determination and documentation that single IRB review is not appropriate, it would add administrative burden and delay the initiation of research, contrary to the goals of this proposed rule. However, we seek comment below on whether FDA should consider adding an analogous exception, in addition to other proposed exceptions, to help address potential challenges to use of a single IRB review model for FDA-regulated cooperative research.

After considering these issues, instead of proposing a broad exemption that would provide for FDA to make case-by-case determinations that use of single IRB review is not appropriate, FDA is proposing specific exceptions that we believe reflect circumstances for which requiring the use of a single IRB for oversight of multisite research may not be appropriate for FDA-regulated research. In these cases, use of single IRB review may not be adequate to provide important expertise for a particular FDA-regulated clinical investigation or may not increase efficiencies for the oversight of certain clinical investigations. The intent of these proposed exceptions is to facilitate FDA-regulated research, minimize administrative burden, and maintain appropriate human subject protections.

1. Cooperative Research For Which More Than Single IRB Review Is Required By Law

The first exception to the requirement for reliance on approval by a single IRB in the revised Common Rule at 45 CFR 46.114(b)(2)(i) includes cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an AI/AN tribe). FDA is proposing this same exception at § 56.114(b)(2)(i).

2. Cooperative Research Involving a Highly Specialized FDA-Regulated Medical Product

FDA is proposing, at § 56.114(b)(2)(ii), an exception from the use of single IRB review for research involving a highly specialized FDA-regulated medical product for which unique, localized expertise is required. For example, for certain highly specialized FDA-regulated medical products, expertise in the use of the product may be limited to only a few specialists at geographically dispersed locations. In such cases, the investigators, research staff, and IRBs associated with the investigational sites would have the critical knowledge and training relevant to the product, and therefore, these IRBs would have the capability to most efficiently conduct initial review and oversee the research, while maintaining appropriate human subject protections. We believe that mandating the use of single IRB review could be an obstacle to initiating important research when the localized expertise is readily available, but none of the IRBs associated with the investigational sites can serve as the single IRB of record. FDA believes that this proposed criterion for exception from use of single IRB review would be met in such a case, although we expect that such exceptions would be rare occurrences.

3. Cooperative Research on Drugs Exempt From the IND Regulations

FDA is proposing, under § 56.114(b)(2)(iii), an exception from mandatory use of single IRB review for research on drugs that is exempt from the requirements for an IND application under § 312.2(b) (21 CFR 312.2(b)). FDA does not require submission of an IND application for certain clinical investigations of lawfully marketed drugs that meet the criteria under § 312.2(b) (see 52 FR 8797, March 19, 1987). Such studies are generally lower risk clinical investigations of products that are lawfully marketed. Unlike clinical investigations that are conducted under the IND requirements,

[11] See, for example, §§ 312.53 and 312.66 (21 CFR 312.53 and 312.66), 21 CFR 320.31, and §§ 812.40, 812.42, 812.43, and 812.110 (21 CFR 812.40, 812.42, 812.43, and 812.110).

[12] See 21 CFR 312.23(a)(6)(iii)(*b*) and 812.20(b)(6).

increased efficiencies leading to earlier initiation of clinical investigations exempt from the IND requirements generally would not provide the benefit of bringing new drugs or new uses of drugs to patients sooner.

4. Cooperative Research on Medical Devices That Meets the Abbreviated Requirements or the Requirements for Exempted Investigations

To facilitate research in accordance with the statutory purpose of section 520(g) of the FD&C Act and avoid unnecessary burden on regulated entities, when FDA issued the IDE regulations at part 812, FDA did not require submission of an IDE application for all categories of device investigations (45 FR 3731 at 3735–3736, January 18, 1980). A device investigation conducted under the abbreviated requirements at § 812.2(b) (21 CFR 812.2(b)) (a nonsignificant risk or ''NSR'' study) is deemed to have an approved IDE and, among other requirements, cannot be an investigation of a significant risk device, as defined at § 812.3(m) (21 CFR 812.3(m)). While IRB approval is required for an NSR study, FDA approval of an IDE application is not. Reducing the level of regulatory controls for these investigations based on the degree of risk was considered appropriate to avoid unnecessary burden and delay in the approval of research without sacrificing human subject protection (see 45 FR 3731 at 3735–3736). In accordance with § 812.2(c), certain device studies are also exempt from the requirements of part 812, with the exception of 21 CFR 812.119 (disqualification of a clinical investigator). The exempt categories outlined at § 812.2(c) include certain studies of legally marketed devices in which the device is used in accordance with its labeled indications (see § 812.2(c)(1) and (2)), and certain studies of diagnostic devices that present low risk to subjects (see § 812.2(c)(3)). The exempt categories also include studies of devices undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk (§ 812.2(c)(4)). In addition, § 812.2(c) clarifies that investigations of the following devices do not require an IDE: (1) a device intended solely for veterinary use; (2) a device shipped solely for research on or with laboratory animals and labeled in accordance with § 812.5(c); and (3) a custom device as defined in § 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. (See § 812.2(c)(5)–(7).)

FDA is proposing an exception from the requirement for single IRB review under § 56.114(b)(2)(iv) for research on medical devices that meets the abbreviated requirements under § 812.2(b) or that meets the requirements for exempted investigations under § 812.2(c), to the extent the exempted investigation would be subject to part 56. This proposed exception would encompass research that presents a lower risk to subjects and, in certain instances, may not involve a therapeutic intervention or invasive procedure (*e.g.,* studies of certain diagnostic devices). The proposed exception would also encompass research that is not focused on bringing new devices to the market for patients. Therefore, the initial administrative burden of establishing cooperative review agreements may not be offset by the anticipated benefits of single IRB review efficiencies, such as improvement in the review and handling of safety reports and faster initiation of research that facilitates the development of new medical products.

In developing this proposed rule, FDA also considered recommendations provided by the Secretary's Advisory Committee on Human Research Protections (SACHRP) to the Secretary of HHS regarding additional categories of research that would be potentially appropriate for exception from the requirement to use a single IRB.[13] FDA is requesting feedback from stakeholders on the following specific circumstances to assist the agency in determining whether additional exceptions to the single IRB review requirement would be warranted.

First, FDA is requesting comment on whether it is appropriate to include an exception for cooperative research for which use of a single IRB is unable to meet the needs of specific populations. Such an exception might apply, for example, to research that involves recruiting members of a distinct patient population or community (*e.g.,* cultural, religious) for which the local perspective is particularly important if the single IRB of record is unable to obtain sufficient supplemental information to consider that community's needs. SACHRP recommended that this exception be considered and provided the following example that illustrates when this exception may be appropriate: There may be an instance where research involves ''an intervention with pregnant women at one site and then follow-up with the neonates at another site. Unless a single IRB had adequate expertise in pregnant women, obstetrical practices, and neonatal medicine, human subject protections might best be served by having the elements relevant to pregnant women reviewed by an IRB that has extensive expertise with that area and the elements relevant to the neonates reviewed by a pediatric IRB.'' [14] In this example, particularly for obstetrical or pediatric research that involves complex medical issues, a single obstetrical or pediatric consultant on an IRB that mainly reviews research in adults may not have the sufficient range of expertise necessary to review the protocol. In these instances, utilizing an IRB with obstetrical expertise and a separate, pediatric IRB that has extensive experience in neonatal research may be in the best interest of the two populations of research subjects.

We request comment on whether a single IRB of record would generally be able to supplement its members' knowledge and experience with additional information or expertise to account for these situations, examples of FDA-regulated research for which these circumstances would apply, and any data on the frequency of how often this situation may occur.

FDA is also requesting comment on including an exception for cooperative research with a small number of investigational sites. SACHRP recommended that research involving five or fewer investigational sites should be considered as potentially appropriate for exception to the single IRB review requirement.[15] FDA is requesting feedback on whether an exception from single IRB review might be warranted for a multisite study with a small number of sites, what the benefits and burdens are for a multisite study with a small number of sites, and what the appropriate threshold should be for the number of sites involved. In addition, we request any specific data that can be provided on the relationship between the number of sites and the value of single IRB review.

In addition, FDA recognizes that situations may arise in which a federally conducted or supported FDA-regulated

[13] Secretary's Advisory Committee on Human Research Protections: Recommendations for IRB Review: Attachment D—Granting Exceptions for Single IRB Review for Multi-Site Research (March 13, 2018) *https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-d-points-to-consider-granting-exceptions-to-requirements-for-single-institutional-review-board-review-for-multi-site-research/index.html.*

[14] Ibid.

[15] Ibid.

clinical investigation would qualify for an exception from single IRB review under this proposed rule but would not qualify for an exception determination issued by a Common Rule Department or Agency pursuant to 45 CFR 46.114(b)(2)(ii) of the revised Common Rule (or vice versa). Both the revised Common Rule and FDA's proposed rule still permit use of a single IRB for review and approval of cooperative research even if an exception applies. However, we are requesting public comment on any impact that such differences in exceptions from the single IRB review requirement may have on stakeholders, and on possible approaches to avoid or minimize any potential negative effects of such differences for stakeholders, such as whether additional exceptions from the proposed single IRB review requirement should be included or whether providing guidance on the application of FDA's proposed exceptions might help avoid or minimize any differences in exceptions.

We also specifically request comment on whether there are unique challenges to use of a single IRB review model for FDA-regulated cooperative research that could not be addressed by FDA's proposed exceptions. For any challenges identified, we seek comment on whether additional exceptions should be included to address them. For example, should FDA consider including an exception analogous to the revised Common Rule's exception at 45 CFR 46.114(b)(2)(ii)? As explained above, we do not believe it is practicable to rely on a broad exemption that would provide for FDA to make case-by-case determinations that use of single IRB review is not appropriate for the particular context as the only means for excepting FDA-regulated cooperative research—other than research for which more than single IRB review is required by law—from the proposed new requirement. The Agency also believes that situations in which use of a single IRB might not be appropriate and in which none of FDA's proposed exceptions apply would be rare. However, we seek comment on whether including an exception that provides for FDA to determine and document that single IRB review is not appropriate for the particular context, in addition to the exceptions FDA has proposed, could help address any such situations and any negative impacts of differences between FDA's proposed exceptions and exceptions available under the revised Common Rule to a Common Rule Department or Agency supporting or conducting cooperative research.

Lastly, FDA is requesting comment on the proposed exceptions and any other criteria that should be considered when assessing whether an exception to the use of single IRB review might be warranted. We also encourage the public to provide examples of any additional types of FDA-regulated clinical investigations that they believe should qualify for such an exception. To help stakeholders comply with these proposed requirements, if finalized, FDA intends to update our guidance on using a centralized IRB review process in multicenter clinical trials.[16]

C. Single IRB Review for Research Not Subject to § 56.114(b)

FDA is proposing new regulatory text at § 56.114(c) to specify that an institution participating in cooperative research that is not subject to the requirement for single IRB review at § 56.114(b) may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort. This proposed regulatory text differs from the revised Common Rule at 45 CFR 46.114(c) by use of the term ''research,'' rather than ''project.'' We believe that the term ''research'' better reflects the terminology used throughout FDA's existing human subject protection regulations. In addition, we note that, even if one of the proposed exceptions under § 56.114(b)(2) applies to a study, use of single IRB review would still be permitted under this proposed provision.

In some cases, FDA-regulated clinical investigations are also Federally conducted or supported and, thus, subject to the revised Common Rule. It is possible that such studies could fit within a proposed exception from FDA's proposed requirement for use of single IRB review but may be required under the revised Common Rule to use single IRB review. In these instances, proposed § 56.114(c) would still permit use of a single IRB for review and approval of the cooperative research.

D. IRB Records

FDA is proposing new regulatory text at § 56.115(a)(8) to require documentation of an institution's reliance on an external IRB for oversight of research. FDA is proposing to require, for research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution, or where appropriate the IRB, must retain documentation specifying the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of part 56 (*e.g.,* in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol). This proposed provision is consistent with the revised Common Rule's requirements at 45 CFR 46.103(e) and 45 CFR 46.115(a)(9). This proposed requirement is necessary for documenting compliance with part 56 to provide a record for FDA's oversight and compliance purposes.

V. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 1 year after the final rule is published in the **Federal Register** to allow the FDA-regulated community that is not subject to the revised Common Rule's single IRB review requirement appropriate time to prepare to implement FDA's proposed single IRB review requirement. FDA is proposing that any such final rule would apply to FDA-regulated cooperative research initially approved by an IRB on or after the proposed effective date. Therefore, ongoing cooperative research that is initially approved by an IRB prior to the proposed effective date would be permitted, but not required, to use a single IRB review process, consistent with FDA's current regulations at § 56.114.

VI. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This proposed rule has been designated an economically significant regulatory action as defined by Executive Order 12866.

[16] See FDA's ''Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials'' (March 2006). Available at: *https://www.fda.gov/media/75329/download.*

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small entities affected by this proposed rule would incur net cost savings, we propose to certify that the rule, if finalized, will not have a significant economic impact on a substantial number of small entities. However, as discussed in the Preliminary Economic Analysis of Impacts (Ref. 5), there is a lack of high quality, comprehensive data regarding the number of small and very small institutions associated with IRBs, as defined by revenue. We have prepared an initial regulatory flexibility analysis and are seeking comment on the data and assumptions used in that analysis.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $165 million, using the most current (2020) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would result in an expenditure in any year that meets or exceeds this amount.

The proposed rule, if finalized, would require any institution located in the United States participating in FDA-regulated cooperative research to rely on approval by a single IRB for that portion of the research that is conducted in the United States, with some exceptions. The proposed rule would harmonize, to the extent practicable and consistent with statutory provisions, FDA's requirements for cooperative research with the requirements of the revised Common Rule in accordance with section 3023 of the Cures Act. This proposed rule should reduce the administrative and coordination costs of conducting FDA-regulated cooperative research by: (1) reducing duplicative reviews; (2) facilitating an earlier start of cooperative research; and (3) reducing the need to reconcile variability in IRB review decisions for cooperative research conducted with a common protocol. Reducing the costs of conducting cooperative research should reduce the costs of FDA-regulated medical product development and facilitate an earlier start of cooperative research, which could contribute to a faster introduction of those products into commercial use. Table 1 summarizes our estimate of the annualized costs and the annualized benefits of the proposed rule, if finalized.

TABLE 1—SUMMARY OF BENEFITS AND COSTS OF THE PROPOSED RULE

[$millions]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized Monetized $millions/year	$453	$117	$1,016	2017	7	10	Benefits are cost savings.
	457	117	1,024	2017	3	10	Benefits are cost savings
Annualized Quantified							
Qualitative	Greater consumer satisfaction and producer profits from reduced medical product development costs and faster commercial introduction.						
Costs:							
Annualized Monetized $millions/year	78	30	134	2017	7	10	
	74	30	127	2017	3	10	
Annualized Quantified							
Qualitative	Education, training, liability coverage, providing local context information, and loss of funding to relying IRBs.						
Transfers:							
Federal Annualized Monetized $millions/year							
	From:			To:			
Other Annualized Monetized $millions/year							
	From:			To:			

Effects:
State, Local or Tribal Government: None.
Small Business: None.
Wages: None.
Growth: None.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 5) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

VII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the PRA (44 U.S.C. 3501–3521). A description of these provisions is given in the *Description* section of this section with an estimate of the annual recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Institutional Review Boards—21 CFR part 56 (OMB Control Number 0910–0130—Revision).

Description: The proposed rule, if finalized, would add § 56.115(a)(8) to require, for FDA-regulated research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, documentation specifying the institution's reliance on the IRB for oversight of the research and the responsibilities each entity will undertake to ensure compliance with part 56 (''IRB reliance agreements''). This might be accomplished in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol. This proposed recordkeeping requirement is necessary for documenting compliance with part 56 to provide a record for FDA's oversight and compliance purposes in cases when IRB oversight is not conducted by an IRB that is operated by the institution (*e.g.,* cooperative research).

Description of Respondents: Respondents to the information collection are IRBs that review and approve clinical investigations regulated by FDA.

We estimate the burden of the information collection as follows:

TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR part 56—Institutional Review Boards	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
56.115(a)(8); Required Documentation	2,520	10	25,200	15	378,000

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

There are approximately 2,520 IRBs that review FDA-regulated research. We estimate that most IRBs will need to set up 10 IRB reliance agreements and that each agreement will require an average of 15 hours to complete.

To ensure that comments on information collection are received, OMB recommends that written comments be submitted through *reginfo.gov* (see **ADDRESSES**). All comments should be identified with the title of the information collection.

In compliance with the PRA (44 U.S.C. 3407(d)), FDA has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the **Federal Register**.

IX. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. We solicit comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov*. References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Flynn K.E, C.L. Hahn, J.M. Kramer, et al. (2013), ''Using Central IRBs for Multicenter Clinical Trials in the United States,'' *PLOS ONE* 8(1): e54999.
2. Greene, S.M. and A.M. Geiger (2006), ''A Review Finds that Multicenter Studies Face Substantial Challenges but Strategies Exist to Achieve Institutional Review Board Approval,'' *Journal of Clinical Epidemiology* 59 (2006) 784–790.
3. Check D.K., K.P. Weinfurt, C.B. Dombeck, et.al. (2013), ''Use of Central Institutional Review Boards for Multicenter Clinical Trials in the United States: A Review of the Literature,'' *Clinical Trials* 10: 560–567.
4. Massett, H.A., S.L. Hampp, J.L. Goldberg, et al. (2018), ''Meeting the Challenge: The National Cancer Institute's Central Institutional Review Board for Multi-Site Research,'' *Journal of Clinical Oncology* 36(8): 819–824.

5. *FDA, Preliminary Economic Analysis of Impacts, Docket No. FDA–2019–N–2175, available at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

List of Subjects in 21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

Therefore, under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 56 be amended as follows:

PART 56—INSTITUTIONAL REVIEW BOARDS

■ 1. The authority citation for part 56 is revised to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c–360f, 360h, 360i, 360j, 360hh–360pp, 360rr–360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262.

■ 2. Revise § 56.114 to read as follows:

§ 56.114 Cooperative research.

(a) Cooperative research covered by these regulations is a clinical investigation that involves more than one institution. In the conduct of cooperative research, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with these regulations.

(b)(1) Any institution located in the United States that is participating in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States.

(2) Research is not subject to paragraph (b)(1) of this section if at least one of the following criteria is met:

(i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe);

(ii) Cooperative research involving a highly specialized FDA-regulated medical product for which unique, localized expertise is required;

(iii) Cooperative research on drugs that meets the exemptions from an investigational new drug application under § 312.2(b) of this chapter; or

(iv) Cooperative research on medical devices that meets the abbreviated requirements under § 812.2(b) of this chapter, or that meets the requirements for exempted investigations under § 812.2(c) of this chapter.

(c) For research not subject to paragraph (b) of this section, an institution participating in cooperative research may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

■ 3. Amend § 56.115 by adding paragraph (a)(8) to read as follows:

§ 56.115 IRB records.

(a) * * *

(8) For research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, documentation specifying the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this part (*e.g.,* in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol).

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Dated: September 23, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

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