DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

INSTITUTIONAL REVIEW BOARDS: COOPERATIVE RESEARCH

Docket No. FDA-2019-N-2175

Preliminary Regulatory Impact Analysis

Initial Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Planning
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

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I. Introduction and Summary

A. Introduction

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.

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 this document, 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.

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 (2022) Implicit Price Deflator for the Gross

Domestic Product. This proposed rule would result in an expenditure in at least one year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The proposed rule, if finalized, would require any institution located in the U.S. participating in FDA-regulated cooperative research to rely on approval by a single institutional review board (IRB) for that portion of the research that is conducted in the U.S., with some exceptions. The proposed rule would harmonize our requirements for cooperative research, to the extent practicable and consistent with statutory provisions, with the requirements of the "Federal Policy for the Protection of Human Subjects" (revised Common Rule)[1] in accordance with section 3023 of the 21st Century Cures Act of December 13, 2016 (the Cures Act) (Public Law 114-255, 130 Stat 1033). 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.

[1] For the purpose of this document, "revised Common Rule" refers to the January 19, 2017 final rule (82 FR 7149), 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).

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	
Benefits	Annualized Monetized $millions/year	$453	$117	$1,016	2017	7%	10 years	Benefits are cost savings
		$457	$117	$1,024	2017	3%	10 years	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 years	
		$74	$30	$127	2017	3%	10 years	
	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 Economic Analysis of Impacts that assesses the impacts of the proposed rule.

C. Definitions

We provide definitions for several terms we use in this document. We note that these definitions only apply to this document.

- Active IRB – An IRB that has current and ongoing oversight of research involving human subjects.
- Ceded Review – The transfer of IRB review and oversight authority to another IRB that accepts responsibility for IRB review and oversight over clinical research.
- Reliance Agreement – For research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, a reliance agreement is the documentation specifying an institution's reliance on the IRB of record for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of 21 CFR part 56.
- Relying IRB – A participating IRB that cedes IRB review to a reviewing IRB for the oversight of research under a reliance agreement.
- Reviewing IRB – The IRB of record with the authority for IRB review and oversight that has been ceded by a participating IRB under the terms of a reliance agreement.
- We/us/our – The Food and Drug Administration.

II. Preliminary Economic Impact Analysis

A. Background

We have historically supported efforts to reduce the regulatory burden of conducting multi-institutional (multisite or cooperative) research. Our regulations related to IRBs, adopted in 1981, allowed for the voluntary use of cooperative IRB review in multi-institutional studies to reduce duplicative reviews of multi-institutional studies (46 FR 8958, January 27, 1981). In 2006, we issued guidance encouraging the voluntary use of a single IRB review process for multicenter clinical studies. Current FDA regulations allow institutions involved in multi-

institutional studies to voluntarily use joint review, to rely upon another qualified IRB, or to use similar arrangements to avoid duplication of effort.

Section 3023 of the Cures Act directs the Secretary of Health and Human Services (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. The Cures Act also requires the Secretary, as appropriate, to ensure that human subject research 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 institutional review board or an institutional review board of an entity other than the sponsor of the research; or (3) use similar arrangements to avoid duplication of effort. Section 3056 of the Cures Act removed the requirement for IRBs overseeing clinical investigations of medical devices to be "local." The revised Common Rule requires that all U.S. institutions engaged in cooperative research rely on a single IRB review, with some exceptions.

Various academic studies have evaluated the burdens of conducting multisite studies and identified duplicative costs and delays as a significant concern. Some researchers have advocated for a single IRB review process. In a meta-analysis of 40 peer reviewed articles regarding the impact of multiple IRB reviews during cooperative research, Greene and Geiger (Ref. 1) identified numerous related but distinct factors that contribute to research delays and unnecessary costs, 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 subject recruitment procedures and participant incentives across sites, possibly affecting enrollment 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, among other factors that contribute to clinical research delays and unnecessary costs. A 2007 survey of IRBs found that between 9 percent and 35 percent of new and continuing IRB reviews at each research site were reviews for multicenter studies (Ref. 2).

B. Need for Regulation

The Cures Act requires the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, to harmonize differences between FDA Human Subject Regulations and HHS Human Subject Regulations. FDA regulations currently provide for the voluntary use of a single IRB review process, and HHS regulations require a single IRB review process for cooperative research, with some exceptions. The initial costs of adopting reliance agreements, without the certainty that all other participating IRBs will adopt reliance agreements, has created a market failure for the voluntary use of a single IRB review process. When the initial coordination costs are borne mostly by the reviewing IRB and the benefits of lower administrative or coordination costs are incurred mostly by the relying IRBs, this inconsistency discourages the use of voluntary single IRB review processes. Without sufficient incentives to adopt and use reliance agreements in a single IRB review process, IRBs, institutions, investigators and sponsors may incur unnecessary costs from (1) duplicative multisite IRB reviews; (2) variation in multisite IRB responses to standard and relatively simple research protocols; and (3) delays obtaining IRB approval from multiple sites.

Uncertainty about whether the terms of a reliance agreement would address local site requirements may contribute to the underutilization of single IRB review processes in a voluntary regime. For example, IRBs may be uncertain about whether and how local requirements regarding language for informed consent documents, participant recruitment, and

the age of assent will be addressed using a single IRB review process. There may also be uncertainty surrounding the reportable events that will be sent to each IRB, or whether there would be local site review of Health Insurance Portability and Accountability Act (HIPAA) requirements (Ref. 3, 4, 5). As a result, initiating the single IRB review process may incur high costs to negotiate a final reliance agreement between a reviewing IRB and multiple relying IRBs. These problems might be compounded by a concern that the single reviewing IRB would not be able to accommodate local variations at each cooperative site, reducing the number of institutions likely to agree to participate in a single IRB review process. Such uncertainty would impose costs and delays that might further discourage the use of a single IRB review process. Even with reliance agreements in place, in a voluntary regime, a relying IRB may continue periodic oversight of the research at their site and conduct potentially duplicative activities and reports. Such actions would add unnecessary administrative costs and discourage the use of a single IRB review process.

The proposed rule would require all institutions to learn and implement a single IRB review process, when applicable. Although a relying IRB would not be prohibited from conducting its own internal review, we expect this duplicative activity to diminish as IRBs and institutions become familiar with and accustomed to initiating reliance agreements and using a single IRB review process. Without a requirement for the use of a single IRB review process for cooperative research, unnecessary costs associated with the voluntary process would be perpetuated (although underlying incentives and other circumstances for institutions would not necessarily change with a single-IRB requirement, thus potentially limiting cost savings).

C. Purpose of the Proposed Rule

The proposed rule, if finalized, would require any institution located in the U.S. 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 U.S., with some exceptions. This would harmonize our requirements for cooperative research, to the extent practicable and consistent with other statutory provisions, with the requirements of the revised Common Rule for cooperative research, as directed by the Cures Act. This proposed rule, if finalized, 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 faster introduction of medical products into commercial use. The proposed rule, if finalized, would benefit consumers and sponsors who develop medical products by reducing development costs, without reducing medical product safety or the protection of human subjects in clinical investigations.

D. Regulatory Familiarization Costs of the Proposed Rule

1. Time to Learn the Rule

The proposed rule would impose one-time costs for affected entities to learn the requirements of the rule. We assume that the members of all covered IRBs would have to spend time to read and understand the proposed rule, if finalized. HHS guidance for estimating this cost is based on the time it takes a manager to read the preamble at a reading speed of 200 to 250 words per minute (Ref. 6). The preamble and proposed regulatory text sections have approximately 11,000 words. We assume that every member of a covered IRB would need to

learn the requirements of the proposed rule. For the purposes of our analysis, we use an IRB and its constituent members to represent an institution. While we acknowledge that sponsors and investigators will also be affected by the proposed rule, if finalized, we characterize costs as being incurred by IRBs due to their primary role in implementing the requirements (e.g., developing reliance agreements).

We assume that the average IRB board is composed of 13 individuals: 1 IRB administrator, 1 IRB chair, 1 IRB staff, and 10 voting members. We estimate that 10 voting IRB members is average and that across IRBs, there is a lower bound of 5 voting members and an upper bound of 20 voting members. We draw from Bureau of Labor Statistics data in the economic analysis of impacts from the revised Common Rule to estimate hourly wage rates for IRB administrators and chairs, IRB voting members, and IRB administrative staff in 2017 dollars (Ref. 7), the latest year for which wage data are available. We use wages for postsecondary education administrators to proxy for the wages of an IRB administrator (Ref. 8), wages of postsecondary health teachers to proxy for the wages of IRB chairs and IRB voting members (Ref. 9), and wages of office and administrative support workers to proxy for IRB administrative staff wages (Ref. 10). We double these hourly wages to account for benefits and other indirect costs (Ref. 11), yielding the fully loaded hourly wages of $106.68 for IRB administrators (= $53.34 x 2), $36.48 for IRB administrative staff (= $18.24 x 2), $118.16 for IRB chairs (= $59.08 x 2), and $118.16 for IRB voting members (= $59.08 x 2). We multiply the estimated number of IRB board members by their corresponding estimated hourly wage rates to yield the estimated hourly wage rate of IRB review. We estimate that the average hourly cost per IRB meeting is approximately $1,442.92 (= $106.68 + $118.16 + ($118.16 x 10) + $36.48), with a lower bound of approximately $852.12 (= $106.68 + $118.16 + ($118.16 x 5) + $36.48) and an

upper bound of approximately $2,624.52 (= $106.68 + $118.16 + ($118.16 x 20) + $36.48). We assume a triangular distribution that consists of these lower and upper bound estimates and a modal estimate of approximately $1,639.85 per IRB meeting per hour. Table 2 summarizes our results. We estimate that there are approximately 11,000 words in the preamble and proposed regulatory text sections of the proposed rule, and that the estimated time burden of reading the rule would be approximately 0.81 hours (= 11,000 / 225 / 60). We multiply the estimated hourly cost per IRB meeting by the estimated number of affected IRBs and the estimated time burden of reading the rule to yield the total cost of learning the rule. We estimate that the one-time cost of learning the rule is approximately $3.4 million (= 2,520 x $1,639.85 x 0.81), with a lower bound of approximately $1.7 million (= 2,520 x $852.12 x 0.81) and an upper bound of approximately $5.4 million (= 2,520 x $2,624.52 x 0.81).

Table 2. Summary of Hourly Costs per IRB Meeting Member

	Wage Rate	Wage Multiplier	Effective Wage Rate	Members per Meeting	Hourly Wage per Meeting
Administrator	$53.34	2	$106.68	1	$106.68
Chair	$59.08	2	$118.16	1	$118.16
Voting Member (Primary)*	$59.08	2	$118.16	10	$1,378.53
Voting Member (Low)*	$59.08	2	$118.16	5	$590.80
Voting Member (High)*	$59.08	2	$118.16	20	$2,363.20
Staff	$18.24	2	$36.48	1	$36.48
Total Hourly Cost per IRB Meeting (Primary)*					**$1,639.85**
Total Hourly Cost per IRB Meeting (Low)*					**$852.12**
Total Hourly Cost per IRB Meeting (High)*					**$2,624.52**

Notes: * Triangular distribution.

E. Baseline Conditions

1. Number of Affected Entities

The affected entities covered by this proposed rule, if finalized, are the active IRBs and

institutions that we regulate and that oversee cooperative research. As in our analysis of the time burden of learning the rule, we use IRBs to proxy for the number of institutions affected by the proposed rule due to data limitations. We estimate there are 2,442 active IRBs regulated by both HHS and FDA. In addition, 78 IRBs are exclusively regulated by FDA (Ref. 12). For this analysis, we assume that every FDA-regulated IRB would be responsible for reviewing at least 1 cooperative research protocol each year. Thus, we estimate the total number of IRBs affected by the proposed rule is 2,520 (= 2,442 + 78).

2. Baseline Costs for the Current Voluntary Single IRB Review Process

For our baseline, we estimate the current annual costs incurred by FDA-regulated IRBs under current regulations while performing their oversight responsibilities of clinical investigations in a voluntary single IRB review regime. To estimate the total baseline costs, we use the average annual number of IRB meetings per FDA-regulated IRB, the average cost of review time in IRB meetings, and the average percentage of time devoted to the review of multisite clinical investigation protocols per meeting. We estimate the total annual baseline cost for the current voluntary single IRB review process such that Total Annual Baseline Cost = [Total covered IRBs] x [(No. of Meetings) / IRB / year] x [(Hours of Review) / Meeting / IRB] x (Total Hourly Cost / IRB) x [Ratio of Multisite Reviews to Total Reviews].

We estimate that an IRB convenes a meeting approximately 14.6 times per year.[2] We estimate that the combined number of hours spent by all IRB members in an IRB meeting is approximately 40 hours, including the time to (1) conduct initial and continuing review of research protocols; (2) review safety reports; (3) prepare notifications regarding reports of

[2] We assume that full IRB review meetings are typical for the types of clinical investigations that FDA-regulated IRBs are most likely to oversee. The weighting that we used is based on the frequency of full meetings held per year.

unanticipated problems involving risks to human subjects or others ("unanticipated problems") (e.g., protocol suspension); (4) prepare notifications regarding reports of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB ("serious or continuing noncompliance"); and (5) perform mandatory recordkeeping or other activities for the oversight of FDA-regulated research. To estimate the cost per meeting per hour, we estimate the wage rate for each of the IRB members that would participate in an average meeting, as shown in Table 2. Based on a survey of 73 IRBs (Ref. 2), we estimate that the lower bound of the ratio of multisite research protocols to total protocols is approximately 9 percent and the upper bound is approximately 35 percent. We estimate the midpoint of these percentages to yield a central estimate of the ratio of multisite protocols to total protocols of 22 percent. As an independent check, we note that the regulatory impact analysis for the revised Common Rule used 30 percent (Ref. 7). We estimate the total baseline cost equals approximately $530.9 million per year [= 2,520 IRBs x (14.6 meetings / year) x (40 hours / meeting) x ($1,639.85 / hour) x 0.22], with a lower bound of approximately $64.9 million per year [= 2,520 IRBs x (9.6 meetings / year) x (35 hours / meeting) x ($852.12 / hour) x 0.09] and an upper bound of approximately $2,041.7 million per year [= 2,520 IRBs x (19.6 meetings / year) x (45 hours / meeting) x ($2,624.52 / hour) x 0.35]. We ask for comment on these estimates.

As an independent check, we note that Sugarman et al. estimated the median cost of IRBs at medical schools in the United States was $741,920 with a range of $402,369 to $1,150,417 per IRB in 2005 dollars (Ref. 13). Adjusting the median cost to 2017 dollars, this median cost equals $942,238 per IRB. We use this median cost to estimate a total baseline cost of approximately $522.4 million (= 2,520 IRBs x $942,238 / IRB x 0.22). Our results are shown in Table 3. We ask for comment on these estimates.

Table 3. Summary of Estimates for the Baseline Costs of the Current Regulatory Regime

	Assumed Distribution	Primary Estimate	Low Estimate	High Estimate	Cited in Literature
Number of IRBs		2,520	2,520	2,520	2,520
Annual Number of IRB Meetings	Normal	14.6	9.6	19.6	
Hours per IRB Meeting	Normal	40	35	45	
Ratio of Multisite Protocols to Total Protocols	Uniform	0.22	0.09	0.35	0.22
Cost per IRB per hour		$1,639.85	$852.12	$2,624.52	
Cost per IRB (based on Ref. 12, $millions)					$0.94
Current Total Annualized Costs ($millions 2017)		**$530.9**	**$64.9**	**$2,041.7**	**$522.4**

F. Costs (Other than Regulatory Familiarization) and Cost Savings of the Proposed Rule

The benefits of the proposed rule, if finalized, come from the cost savings of reducing the administrative and coordination costs to conduct 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. To estimate the cost savings, we estimate the total costs to comply with a mandatory single IRB review process and compare those costs with our estimate of the current baseline costs. The costs to comply with the proposed rule, if finalized, include the costs to prepare and adopt the initial reliance agreements and to perform the tasks required by the reliance agreements or by other applicable FDA regulations. These tasks include recording the education and training of the IRB members, performing the notification of changes in IRB registration, performing the initial and continuing review of the clinical investigation protocols, notifying participating investigators and research sites of reviewing IRB decisions, documenting

IRB activities, and documenting the terms of the reliance agreements in accordance with proposed § 56.115(a)(8).

We anticipate the additional cost for adopting reliance agreements will include the staff time to review and implement the agreements. As in the rest of our analysis, we use IRBs to represent institutions affected by the proposed rule. To estimate the costs to review and implement reliance agreements, we assume that every covered IRB will require an average of 10 different reliance agreements to cover a variety of different research protocols and that it will take 15 hours to review and implement the agreements, based on the economic analysis of impacts from the revised Common Rule (Ref. 7). However, our estimate differs slightly from the economic analysis of impacts from the revised Common Rule, which assumed that each agreement would require 10 hours of institution legal staff review time and 5 hours of IRB administrator time to complete (Ref. 7). For this analysis, we assume the review and administration of the reliance agreement would require 15 hours for a committee, composed of an IRB administrator, the IRB chair, two legal staff and one IRB administrative staff, working together (Ref. 7). The cost of adopting reliance agreements will be a one-time cost. Based on the development of platforms that provide master IRB reliance agreements,[3] we anticipate that reliance agreements will become standardized over time, which would reduce the expense and review times to adopt future agreements. Table 4 summarizes our estimate for the labor costs to review per hour.

Table 4. Summary of Hourly Labor Costs to Review and Adopt Reliance Agreements

	Wage Rate	Wage Multiplier	Hourly Wage Rate	Mean Staff per Review	Total Hourly Wage Rate
IRB Administrator	$53.34	2	$106.68	1	$106.68
IRB Chair	$59.08	2	$118.16	1	$118.16

[3] For example, SMART IRB (the Streamline, Multisite, Accelerated Resources for Trials IRB Reliance platform), https://smartirb.org/.

IRB Legal Staff	$68.22	2	$136.44	2	$272.88
IRB Administrative Staff	$18.24	2	$36.48	1	$36.48
Total Hourly Cost Per IRB					**$534.20**

We anticipate some turnover and growth in the number of IRBs, the periodic adoption of new types of reliance agreements, and revisions to existing agreements over time. To account for this, we assume IRBs would incur annual additional recurring costs equaling about ten percent of the one-time costs. We ask for comment on this estimate. Table 5 summarizes our estimate for the one-time and recurring costs of adopting and reviewing reliance agreements.

Table 5. One-time and Recurring Additional Cost for Preparing, Adopting, and Documenting Reliance Agreements ($millions 2017)

	Assumed Distribution	Primary Estimate	Low Estimate	High Estimate
Number of IRBs		2,520	2,520	2,520
Reliance Agreements / Reviewing IRB	Normal	10	5	15
Hours to Prepare, Adopt, and Document / Reliance Agreement	Normal	15	10	20
Labor Cost of Reliance Agreement per Hour		$534.20	$534.20	$534.20
Total One-time Cost		**$201.9**	**$67.3**	**$403.9**
Total Recurring Costs (10% of one-time costs)		**$20.2**	**$6.7**	**$40.4**

We estimate IRBs would incur additional costs to comply with the terms of the reliance agreements. We expect that reviewing IRBs would spend more time reviewing clinical investigation protocols than they ordinarily would to comply with the terms of typical reliance agreements, and that relying IRBs would only review the protocols sporadically. For our estimate of the number of FDA-regulated clinical investigations that would be subject to the mandatory single IRB review process, we reviewed the number of U.S. clinical trials submitted to ClinicalTrials.gov and conducted under an IND or IDE for 2015, 2016, and 2017, excluding trials funded by NIH and adjusting for the number of multisite clinical trials, yielding an average

of approximately 662 multisite clinical investigations each year. We assume reviewing IRBs would devote an additional 10 hours per protocol performing reliance agreement-related duties when reviewing current and ongoing multisite protocols, with a lower bound of 5 additional hours per protocol and an upper bound of 15 additional hours per protocol to account for the wide variety of protocols and types of reliance agreements. Table 6 summarizes our estimate of the additional cost per year that reviewing IRBs would incur to review the protocols for multisite clinical investigations under reliance agreements. We ask for comment on this estimate.

Table 6. Additional Cost to Review Multisite Clinical Investigations by Reviewing IRBs

Reviewing IRB Review of Clinical Investigation Protocols	Assumed Distribution	Primary Estimate	Low Estimate	High Estimate
Cooperative Research Protocols Per Year	Normal	661.83	361.83	961.83
Additional Hours to Review Per Protocol	Normal	10	5	15
Hourly Cost of IRB	Triangular	$1,639.85	$852.12	$2,624.52
Total Annually Recurring Costs ($millions 2017)		**$10.9**	**$1.5**	**$37.9**

We assume relying IRBs may still perform sporadic ongoing review of the multisite protocols for research conducted at their participating institution, but that the number of reviews will decrease over time as relying IRBs become more familiar with cooperative research IRB protocols. Specifically, we estimate that in the second year after publication of the final rule, ongoing reviews will decrease to 80 percent of the previous number of reviews and will decrease by 20 percent ever year until the fifth year after publication of the final rule. This estimate acknowledges that some relying IRBs may always prefer to conduct review, and we request comment on these estimates. We estimate that reviews will be approximately 1 hour per protocol, with a range of 0 to 2 hours for each protocol; we assume this value takes a uniform distribution with a central estimate of 1 hour. Table 7 summarizes our estimate of the annually

recurring additional costs for relying IRBs to review ongoing multisite clinical investigations at their sites. We ask for comments on these estimates.

Table 7. Recurring Additional Cost to Review Ongoing Clinical Investigations by Relying IRBs ($millions 2017)

Ongoing Review of Protocols	Assumed Distribution	Primary Estimate	Low Estimate	High Estimate
Cooperative Research Protocols Per Year (Year 1)	Normal	661.83	361.83	961.83
Cooperative Research Protocols Per Year (Year 2)	Normal	529.47	289.46	769.46
Cooperative Research Protocols Per Year (Year 3)	Normal	397.10	217.10	577.10
Cooperative Research Protocols Per Year (Year 4)	Normal	264.73	144.73	384.73
Cooperative Research Protocols Per Year (Years 5 - 10)	Normal	132.37	72.37	192.37
Hours to Review Per Protocol Per Reviewing IRB	Uniform	1	0	2
Hourly cost of IRB		$1,639.85	$852.12	$2,624.52
Annual Cost of Reviewing Protocols (Year 1)		$1,085,310	$308,323	$2,524,342
Annual Cost of Reviewing Protocols (Year 2)		$868,248	$246,658	$2,019,474
Annual Cost of Reviewing Protocols (Year 3)		$651,186	$184,994	$1,514,605
Annual Cost of Reviewing Protocols (Year 4)		$434,124	$123,329	$1,009,737
Annual Cost of Reviewing Protocols (Years 5 - 10)		$217,062	$61,665	$504,868
Net Present Value ($millions, 3%)		**$3.9**	**$1.1**	**$9.1**
Net Present Value ($millions, 7%)		**$3.4**	**$1.0**	**$8.0**
Annualized Costs ($millions, 3%, 10 years)		**$0.5**	**$1.3**	**$1.1**
Annualized Costs ($millions, 7%, 10 years)		**$0.5**	**$1.4**	**$1.1**

Reviewing and relying IRBs would continue recording the education and training of their IRB members and performing notifications of any change in their IRB registration. Reviewing

IRBs would continue to notify participating IRBs about clinical investigation decisions, unanticipated problems, serious or continuing noncompliance, and perform recordkeeping activities. We assume that most covered IRBs already perform these activities. We show the percentages that are likely to incur an additional cost for these activities and the estimated time burden associated with these activities based on the judgement of our experts with extensive experience as members of IRBs that review FDA-regulated clinical investigations. We also estimate that approximately 10 percent of IRBs may incur additional costs for miscellaneous recordkeeping. Table 8 presents the estimated costs of recurring notifications and recordkeeping. We ask for comment on these estimates.

Table 8. Additional Cost for Recurring Notification and Recordkeeping Costs ($millions 2017)

Notifications and Recordkeeping Costs	Assumed Distribution	Primary Estimate	Low Estimate	High Estimate
Cooperative Research Protocols Per Year	Normal	661.83	361.83	961.83
Notification of Reviewing IRB Decisions Per Relying IRB (Hours)	Normal	1	0	2
Hourly IRB Cost		$1,639.85	$852.12	$2,624.52
Total Annually Recurring Notification Costs		**$1.1**	**$0**	**$5.0**
Cooperative Research Protocols Per Year	Normal	661.83	361.83	961.83
Annual Hours for Notification Per Protocol Per IRB	Normal	5	0	10
Percentage Submitting Notification		75%	75%	75%
Hourly IRB Cost		$1,639.85	$852.12	$2,624.52
Total Annually Recurring Unanticipated Problems Notification Costs		**$4.1**	**$0**	**$18.9**
Cooperative Research Protocols Per Year	Normal	661.83	361.83	961.83
Annual Hours for Notification Per Protocol	Normal	10	0	20
Percentage Submitting Notification		30%	30%	30%
Hourly IRB Cost		$1,639.85	$852.12	$2,624.52
Total Annually Recurring Serious/Continuing Noncompliance Notification Costs		**$3.3**	**$0**	**$15.1**
Total Annually Recurring Miscellaneous Recordkeeping Costs		**$4.2**	**$0**	**$5.9**

Total Additional Notification and Recordkeeping Costs		**$12.7**	**$0**	**$44.9**

Some IRBs have stated concern with assuming a relying IRB role because of perceived liability issues of ceding review oversight to another institution (Ref. 14). Under the proposed rule, should it become finalized, some relying IRBs may choose to conduct additional legal review in light of such concerns. To proxy for this additional cost, we calculate a time burden of legal review using the hourly wage rate for legal review (Ref. 7). We estimate that approximately 50 of new cooperative research protocols will undergo additional legal review, with a lower bound of approximately 25 percent and an upper bound of 100 percent. We estimate that the time burden of legal review will be approximately 80 hours per new protocol, with a lower bound of approximately 40 hours and an upper bound of approximately 120 hours. Table 9 presents the estimated costs of this additional legal review by relying IRBs. We ask for comment on these estimates.

Table 9. Recurring Additional Cost of Additional Legal Review by Relying IRBs ($millions 2017)

	Primary Estimate	Low Estimate	High Estimate
Cooperative Research Protocols Per Year	661.83	361.83	961.83
Percent of Protocols To Undergo Additional Legal Review	50	25	100
Number of Protocols Reviews Per Year	330.92	90.46	961.83
Hourly Wage Rate of Legal Review	$272.88	$272.88	$272.88
Time Burden of Additional Legal Review (hours)	80	40	120
Total Annually Recurring Costs	**$7.2**	**$1.0**	**$31.5**

Table 10 summarizes our estimates for the total (additional) costs to comply with the proposed rule.

Table 10. Summary of the Primary Estimate of the Total Compliance Costs ($millions 2017)

Cost Component	Primary Estimate

One-time Costs	
Cost to Learn Rule	$3.4
Preparation, Review and Administration of Reliance Agreements	$201.9
Total One-time Costs	**$205.3**
Recurring Costs (All years)	
Protocol Review/Reviewing IRB	$10.9
Notifications of Reviewing IRB Decisions	$1.1
Notifications of Unanticipated Problems	$4.1
Notification of Serious/Continuing Noncompliance	$3.3
Miscellaneous Recordkeeping	$4.2
Additional Legal Review by Relying IRBs	$7.2
Total Recurring Costs (All years)	**$30.8**
Total Recurring Costs (Year Two and onward)	
New or Revised Reliance Agreements	$20.2
Ongoing Review of Protocols by Relying IRB	$0.5
Total Recurring Costs (Year Two and Onward)	**$50.9**

We estimate that the present value of the cost to comply with the proposed rule is approximately $544.8 million discounted at 7 percent and approximately $632.8 million discounted at 3 percent, incorporating a Monte Carlo simulation. Over 10 years, we estimate that the annualized additional costs to comply with the proposed rule would equal approximately $77.6 million discounted at 7 percent and approximately $74.2 million discounted at 3 percent, as shown in Table 11.

Table 11. Summary of the Present Value and Annualized Costs over 10 Years ($millions 2017)

Year	One-time Costs	Annual Recurring Costs	Net Undiscounted	Discounted (7%)	Discounted (3%)
1	$205.7	$24.6	$230.0	$214.9	$223.3
2		$54.2	$54.2	$47.3	$51.1
3		$54.2	$54.2	$44.2	$49.6
4		$54.2	$54.2	$41.3	$48.1
5		$54.2	$54.2	$38.6	$46.7
6		$54.2	$54.2	$36.1	$45.4
7		$54.2	$54.2	$33.7	$44.0
8		$54.2	$54.2	$31.5	$42.8
9		$54.2	$54.2	$29.5	$14.5
10		$54.2	$54.2	$27.5	$40.3

Present Value				**$544.8**	**$632.8**
Annualized				**$77.6**	**$74.2**

G. Non-Quantified Costs

Because of data limitations, we recognize that there are potential sources of costs to IRBs that we cannot estimate quantitatively. These may include expanded electronic systems capacity to facilitate external access to data, increased staffing and consulting needs, additional education and training for IRB members, and liability coverage. We request comment on these potential sources of initial or ongoing costs to IRBs. We also acknowledge that there may be switching costs associated with functioning as a relying IRB under the single IRB review model described in the proposed rule. For example, an IRB that transitions to functioning primarily as a relying IRB may experience a decrease in funding or revenue or incur costs related to providing information on local context to the single IRB of record. We request comment on these and other costs or perceived barriers that may cause potential relying IRBs to resist switching to a single IRB review model for FDA-regulated cooperative research.

H. Summary of Quantified Costs and Benefits

To estimate the cost saving benefits, we subtract the difference between the total baseline costs, shown in Table 3 and the total additional costs to comply with the proposed rule, if finalized, shown in Table 11. We estimate that the proposed rule, if finalized, will generate annualized net cost savings of $375.7 million (= $453.3 million - $77.6 million) discounted at 7 percent and $382.5 million (= $456.7 million - $74.2 million) discounted at 3 percent as shown in Table 12.

Table 12. Summary Estimate of the Costs and Cost Saving Benefits ($millions 2017)

	Annualized (7%)	Annualized (3%)
Costs	$77.6	$74.2

Cost Savings	$453.3	$456.7
Net Cost Savings	$375.7	$382.5

I. Non-Quantified Cost Saving Benefits

We also expect that the proposed rule will generate benefits that we cannot quantify in this analysis. A mandatory single IRB review process would facilitate an earlier start for cooperative research. Economic theory suggests facilitating an earlier start should facilitate lower costs for clinical investigations, although we cannot quantify this cost saving benefit. One study compared the approval time required for a single IRB review process with a process of local IRB review and approvals in an ongoing multicenter randomized trial and found the single reviewing IRB approved a study in a median of 27 days, compared to a median of 66 days with review by multiple local IRBs. The authors also noted the total time from protocol receipt to IRB approval varied markedly across sites (Ref. 3). Numerous studies have shown IRB approval times vary widely in multisite trials and that iterative reviews are often needed to achieve a final approval for all the sites (Ref. 1). With more study sites, IRB approval times would likely increase, on average. Avoiding unnecessary delays to achieve IRB approval would reduce the costs for conducting clinical investigations.

A mandatory single IRB review process should also reduce the costs of conducting cooperative research by reducing the need to reconcile variability in IRB review decisions for research conducted with a common protocol. For example, a change to the common protocol or informed consent required by one site's IRB could mean additional reviews by all other IRBs, resulting in delay in initiating a study. In addition, if the requirements for recruitment vary between sites, the difficulty and cost for recruiting subjects with the condition of interest would rise, and in some cases, may affect the generalizability of results. We are unable to quantify the

cost-saving benefits from avoiding unnecessary variability, but it could be significant. We request comment on these potential cost-savings.

J. Distributional Effects

The proposed rule, if finalized, would not have significant distributional effects. We expect that the likely costs and net costs saving benefits would be widely shared by the covered IRBs and, over time, by the investigators and the sponsors of the clinical investigations.

K. International Effects

The proposed rule, if finalized, would only apply to cooperative research conducted in the U.S. Foreign sponsors of cooperative research in the U.S. would benefit from the net cost savings. We lack sufficient data to estimate the number of foreign sponsors of domestic cooperative research but the rule, if finalized, would not have an adverse effect on foreign sponsors' ability to conduct research in the U.S., nor would it adversely affect or crowd out domestic researchers. By reducing the cost to conduct clinical investigations in the U.S., the rule should facilitate more foreign investment in the domestic medical product research.

L. Uncertainty and Sensitivity Analysis

The sources of uncertainty in our cost estimates are a lack of data that directly identify the full cost to (1) comply with the current requirements; and (2) comply with the proposed rule, if finalized. For our estimate for the current costs to comply, we lack data for the exact number of multisite clinical investigations, the number of new reliance agreements or the hours to prepare and implement the agreements, the time that IRBs will devote to the oversight of new and continuing clinical investigations, and for the time that would be needed for the various notifications and recordkeeping. To characterize the uncertainty in our estimates, we use

simulations based on ranges between our high and low estimates and our assumed distribution for each variable, as shown in Table 13.

Table 13. Major Sources of Uncertainty

	Assumed Distribution	Low Estimate	High Estimate
Baseline Number of IRB Meetings / Year	Normal	10	20
Baseline Hours of Review / IRB Meeting / IRB	Normal	35	45
New Multisite Protocols / Year	Normal	362	962
Reliance Agreements	Normal	5	15
Hours to Prepare and Implement Reliance Agreements	Normal	10	20
Ratio of Relying IRBs / Reviewing IRBs	Normal	5	15
Hours of Oversight by Reviewing IRBs	Normal	5	15
Reviewing IRB Decision Notifications	Uniform	0	2
Notification of Unanticipated Problems	Uniform	3	7
Notification of Serious/Continuing Noncompliance	Uniform	0	20

Using simulations and the ranges and the distributions shown in Table 12, we estimate the baseline costs and the costs under the proposed rule, if finalized, to comply and the net cost savings at the 5th and the 95th percentile of likelihood. We estimate a range for the annualized net cost savings of between approximately $122.9 million and $970.5 million. We show a summary of the results of our computer simulation at the 5th percentile in Table 14 and of the results in the 95th percentile in Table 15.

Table 14. Simulation Results at 5th Percentile ($millions 2017)

5th Percentile	Present Value (7%)	Present Value (3%)	Annualized (7%)	Annualized (3%)
Baseline Costs	$1,077.2	$1,308.3	$153.4	$153.4
Costs with Proposed Rule	$214.2	$259.5	$30.5	$30.4
Net Cost Savings	$863.0	$1,048.8	$122.9	$123.0

Table 15. Simulation Results at 95th Percentile ($millions 2017)

95th Percentile	Present Value (7%)	Present Value (3%)	Annualized (7%)	Annualized (3%)
Baseline Costs	$7,732.0	$9,390.6	$1,100.9	$1,100.9

Costs with Proposed Rule	$970.8	$1,112.4	$138.2	$130.4
Net Cost Savings	$6,761.2	$8,278.2	$962.6	$970.5

M. Analysis of Regulatory Alternatives to the Proposed Rule – Require Relying IRBs to Perform at least some Annual Oversight of Clinical Investigations

We have identified and assessed one regulatory alternative to the proposed rule. Under this alternative regulatory option, relying IRBs would still be required to provide at least some ongoing annual oversight of the clinical investigations at their research sites.

To assess the impact of this regulatory alternative, we estimate that relying IRBs would spend approximately 2 hours per protocol on continued review, with an upper bound of 3 hours and a lower bound of 1 hour. Additionally, we estimate that IRBs will spend approximately 10 hours per protocol on the notifications regarding unanticipated problems, with a lower bound of 5 hours and an upper bound of 15 hours. Finally, our regulatory alternative estimates that IRBs will spend approximately 20 hours per protocol on the notifications regarding serious or continuing noncompliance, with an upper bound of 30 hours and a lower bound of 10 hours. With this alternative, our estimate for the annualized cost-saving benefits is approximately $362.5 million discounted at 7 percent and approximately $369.2 million discounted at 3 percent as shown in Table 16. While there remains a cost-saving benefit under this option, the net cost saving benefit is significantly less than for the proposed rule, if finalized.

Table 16. Costs and Cost Savings Benefits for the Regulatory Alternative ($millions 2017)

	One-Time Costs	Annualized (7%)	Annualized (3%)
Costs	$205.7	$84.2	$80.9
Cost Savings		$446.7	$450.1
Net Cost Savings		**$362.5**	**$369.2**

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies 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 this document, 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 per SBA definition. We have prepared an Initial Regulatory Flexibility Analysis and are seeking comment on the data and assumptions used in that analysis. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

The small entities most likely to be affected by the proposed rule, if finalized, are the medical institutions, primarily medical and surgical hospitals, affiliated with the covered IRBs. To estimate the number of affiliated small hospitals, we use Census Bureau data with the NAICS code 622110 (Ref. 15), and the Small Business Administration definition for a small hospital of $38.5 million in annual revenues (Ref. 16). We estimate the number of small medical and surgical hospitals is 2,838 out of a total of a total of 6,821 hospitals, or 42 percent are small. We therefore estimate that the number of small entities covered by the proposed rule would be approximately 1,048 (= 2,838 / 6,821 x 2,520) IRBs. As in our estimation of the full costs of the proposed rule, we use the number of affected small IRBs as a proxy for the number of small institutions. Because of the lack of high quality, comprehensive data on IRBs, we are unable to examine the revenues of IRBs, and we request comment on whether such data are available.

We estimate that small entities affected by the proposed rule will act as relying IRBs and incur costs related to learning the rule, adopting of reliance agreements, and the subsequent recordkeeping and notification requirements. These costs are estimated in the same manner as the full costs of reliance agreement adoption (Table 5), ongoing review (Table 7), notification and recordkeeping (Table 8), and additional legal review (Table 9). We estimate that the fully-loaded hourly wage cost per small IRB is equal to that of the average IRB, with an estimated cost of approximately $1,639.85 per IRB (Table 2) and approximately $534.20 for reliance agreement (Table 4). We request comment on these estimates.

Table 17 presents a summary of the primary cost estimates for small entities. We estimate that the one-time costs of the proposed rule for small entities are approximately $85.4 million. We estimate that annually recurring costs of the proposed rule to small entities over 10 years are approximately $13.3 million, with additional recurring costs after the first year of approximately $33.5 million.

Table 17. Summary of the Primary Estimate of Total Compliance Costs for Small Entities ($millions 2017)

Cost Component	Primary Estimate
One-time Costs	
Cost to Learn Rule	$1.4
Preparation, Review and Administration of Reliance Agreements	$84.0
Total One-time Costs	**$85.4**
Recurring Costs (All years)	
Review of New Protocols by Reviewing IRBs	$10.9
Notifications of Reviewing IRB Decisions	$1.1
Notifications of Unanticipated Problems	$4.1
Notification of Serious/Continuing Noncompliance	$3.3
Miscellaneous Recordkeeping	$1.8
Additional Legal Review by Relying IRBs	$3.0
Total Recurring Costs (All years)	**$24.2**
Total Recurring Costs (Year Two and onward)	
New or Revised Reliance Agreements	$8.4
Ongoing Review of Protocols by Relying IRB	$1.1
Total Recurring Costs (Year Two and Onward)	**$33.7**

Table 18 summarizes the estimated costs and cost savings of the proposed rule for small entities. The estimated annualized costs of the proposed rule over 10 years are approximately $48.9 million in 2017 dollars, at a 7 percent discount rate. At a 3 percent discount rate, annualized costs are approximately $47.6 million. We divide the estimated costs of the proposed rule for small entities by the number of covered small entities to yield the net cost savings per small entity. We estimate that the annualized costs of the proposed rule are approximately $46,648 (= $48.9 million / 1,048) per small entity in 2017 dollars at a 7 percent discount rate. At a 3 percent discount rate, annualized costs are approximately $45,406 (= $47.6 million / 1,048) per small entity. Any industry trade group support with training materials and instruction would further reduce the cost to comply. Further, our estimated average cost savings exceed the associated estimated costs.

Estimated annualized cost savings of the proposed rule are approximately $172.0 million at a 7 percent discount rate and approximately $173.3 million at a 3 percent discount rate. This yields annualized net cost savings for small entities of approximately $123.1 million in 2017 dollars, at a 7 percent discount rate. At a 3 percent discount rate, annualized net cost savings for small entities are approximately $125.7 million. We estimate that the annualized net cost savings of the proposed rule are approximately $117,392 (= $123.1 million / 1,048) per small entity in 2017 dollars at a 7 percent discount rate. At a 3 percent discount rate, annualized costs are approximately $119,876 (= $125.7 million / 1,048) per small entity. We therefore propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. These estimates are summarized in Table 18.

Table 18. Summary Estimate of the Costs and Cost Saving Benefits for Small Entities (2017$)

	Annualized (7%)	Annualized (3%)
Costs (millions)	$48.9	$47.6

Costs per Small Entity	**$46,648**	**$45,406**
Cost Saving Benefits (millions)	$172.0	$173.3
Net Cost Savings (millions)	**$123.1**	**$125.7**
Net Cost Savings per Small Entity	**$117,392**	**$119,876**

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane; Rm. 1061, Rockville, MD 20852 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.

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