DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Protection of Human Subjects and Institutional Review Boards

Docket No. FDA-2021-N-0286

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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

Executive Summary

The Food and Drug Administration (FDA, the Agency, we), proposes to modernize, simplify, and enhance the current system for oversight of FDA-regulated human subject research. We propose to harmonize certain sections of FDA regulations on human subject protection (21 CFR part 50) and institutional review boards (IRBs) (21 CFR part 56), to the extent practicable and consistent with other statutory provisions, with the revised Common Rule, in accordance with section 3023 of the 21st Century Cures Act. We also propose minor technical and editorial changes. We believe that the proposed changes, if finalized, will help ensure clarity and enhance both human subject protection and the IRB review process. In addition, harmonization with the revised Common Rule would reduce regulatory burden for IRBs, sponsors, and investigators. The primary quantifiable benefit of the proposed rule is a decreased time burden to IRBs, investigators, and sponsors of clinical investigations from increased harmonization with the revised Common Rule. Quantifiable costs include the development of informed consent documents and additional recordkeeping burdens. The estimated annualized cost savings of the proposed rule range from approximately $22 to $249 million in 2018 dollars, with a central estimate of approximately $68 million, discounted at 7 percent over 10 years. At 3 percent, estimates of annualized cost savings range from approximately $22 to $249 million, with a central estimate of approximately $68 million. Estimated annualized costs of the proposed rule range from approximately $0.7 million to $3.0 million, with a central estimate of approximately $1.4 million, discounted at 7 percent. At 3 percent, estimates of annualized costs range from approximately $0.6 million to $2.6 million, with a central estimate of approximately $1.3 million.

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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). We believe that this proposed rule is 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 estimated cost savings of the proposed rule are greater in magnitude than estimated costs, and because we do not expect the effects of the rule to affect entities by size, 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 not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

If finalized, the proposed rule would: (1) revise the content, organization, and presentation of information included in the informed consent form and process to facilitate a prospective subject's decision about whether to participate in a clinical investigation[1]; (2) add new basic and additional elements of informed consent; (3) add a provision allowing IRBs to eliminate continuing review of some research; (4) revise IRB recordkeeping requirements for certain determinations related to the need for continuing review; and (5) add or modify some definitions. The rule also proposes to revise FDA's regulations on investigational device exemptions (IDEs, 21 CFR part 812) to clarify and update the requirements for submission of progress reports for clinical investigations of devices.

The proposed rule would harmonize certain aspects of FDA's regulations on IRBs and informed consent processes, 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)[2] 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).

[1] The term "clinical investigation" is defined in current 21 CFR 50.3(c) and 21 CFR 56.102(c). For purposes of this document, the terms "clinical investigation," "clinical trial" and "trial" are used synonymously.

[2] For the purposes of this document, the phrase "revised Common Rule" refers to the final rule (82 FR 7149, January 19, 2017), modified by the interim final rule that delayed the effective date and general compliance date (83 FR 2885, January 22, 2018) and the 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 proposed rule should reduce the costs of conducting clinical investigations by harmonizing informed consent and certain continuing review processes for FDA-regulated research with the those required by the revised Common Rule. The proposed rule will also generate costs that we estimate will be relatively smaller than expected cost savings in the form of additional time spent learning the rule, developing new informed consent documents in line with the rule, and complying with the revised recordkeeping requirements related to continuing review. We also expect benefits that we do not estimate explicitly due to data limitations, including increased efficiency of clinical investigations and medical product development and improved human subject knowledge by providing subjects with clearer information regarding clinical investigations. Table 1 summarizes our estimates of the annualized costs and annualized benefits (in the form of cost savings) of the proposed rule.

The benefits of the proposed rule take the form of quantified net cost savings (cost savings minus costs) and non-quantified benefits. We estimate that the benefits of the proposed rule (in the form of cost savings) are approximately $68 million annually in 2018 dollars, with a lower bound of approximately $22 million and an upper bound of approximately $249 million, discounted at 7 percent over 10 years. When discounted at 3 percent, estimated benefits are approximately $68 million annually, with a lower bound of approximately $22 million and an upper bound of approximately $249 million. We also expect benefits in the form of cost savings from increased efficiency in medical product innovation and improved human subject knowledge. We estimate that the costs of the proposed rule are approximately $1.4 million annually in 2018 dollars, with a lower bound of approximately $0.7 million and an upper bound of approximately $3.0

million, discounted at 7 percent over 10 years. When discounted at 3 percent, estimated costs are approximately $1.3 million annually, with a lower bound of approximately $0.6 million and an upper bound of approximately $2.6 million. These estimates are summarized in Table 1.

Table 1: Summary of Benefits, Costs and Distributional Effects of Proposed Rule (millions$)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year	$68	$22	$249	2018	7%	10 years	Benefits are Cost Savings
		$68	$22	$249	2018	3%	10 years	Benefits are Cost Savings
	Annualized Quantified					7%		
						3%		
	Qualitative	Increased efficiency in medical product innovation and improved human subject knowledge by providing subjects with clearer information regarding clinical investigations						
Costs	Annualized Monetized $millions/year	$1.4	$0.7	$3.0	2018	7%	10 years	
		$1.3	$0.6	$2.6	2018	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: Small Business: Wages: Growth:							

II. Preliminary Economic Analysis of Impacts

A. Background

The purpose of this proposed rule is to modernize, simplify, and enhance the current system for oversight of FDA-regulated human subject research. The proposed rule, if finalized, would harmonize certain sections of FDA's regulations on human subject protection (21 CFR part 50) and IRBs (21 CFR part 56), to the extent practicable and consistent with other statutory provisions, with the revised Common Rule in accordance with section 3023 of the Cures Act. This rule also proposes to revise FDA's regulations on IDEs to clarify and update the requirements for submission of progress reports for clinical investigations of devices.

On January 19, 2017, HHS announced revisions to modernize, strengthen, and make the Common Rule more effective.[3] 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 the regulated community.[4]

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 purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections across federal departments and agencies.[5] We expect that harmonization of some sections of FDA's Human Subject Regulations with those of HHS, as described in this proposed

[3] 82 FR 7149, January 19, 2017.
[4] 82 FR 7149, January 19, 2017.
[5] 80 FR 53931 at 53935, September 8, 2015.

rule, will increase the efficiency of FDA-regulated clinical investigations and promote the development of FDA-regulated medical products. We also expect that the proposed rule would benefit potential human research subjects by providing clearer information regarding clinical investigations.

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 the FDA Human Subject Regulations and HHS Human Subject Regulations. Prior to the most recent revision to the Common Rule, FDA regulations regarding the protection of human subjects have been generally consistent with the Common Rule, with some exceptions arising from differences in FDA's mission and statutory authority.

Without this proposed harmonization, IRBs, investigators, and sponsors may incur costs from unnecessary differences between FDA's current regulations regarding informed consent and continuing review and the Common Rule provisions. While the proposed rule is expected to induce some costs, the cost-saving benefits of the rule take the form of reduced time burdens to IRBs, investigators, and sponsors. Reducing such time burdens should increase the efficiency of affected entities, which will allow IRBs, investigators, and sponsors to allocate additional resources to the review of higher risk research or the development of FDA-regulated products.

C. Purpose of the Proposed Rule

The purpose of this proposed rule is to modernize, simplify, and enhance the current system for oversight of FDA-regulated human subject research. The proposed rule, if finalized, would, among other things, revise the content, organization, and

presentation of information in informed consent forms and allow IRBs to eliminate continuing review of research in some circumstances. This would harmonize certain informed consent and continuing review requirements for FDA-regulated clinical investigations with certain requirements of the revised Common Rule, to the extent practicable and consistent with other statutory provisions, as directed by the Cures Act. We expect that the increased efficiency from harmonization of such requirements with the revised Common Rule will benefit IRBs, investigators, and sponsors in the form of reduced time burdens related to informed consent and continuing review procedures. The proposed rule, if finalized, would also benefit the consumers of medical products and the sponsors that develop them by reducing inefficiencies in product development without reducing the safety or the protection of human subjects in clinical investigations.

D. Costs of the Proposed Rule

If finalized, we estimate that the proposed rule will generate costs related to (1) reading and learning the rule; (2) developing informed consent forms that satisfy the new requirements in the rule; and (3) adding recordkeeping requirements for certain determinations related to the need for continuing review.

1. Learning the Proposed Rule

The proposed rule, if finalized, would impose one-time costs for affected entities to learn the requirements of the rule. We estimate that IRB members, IRB legal staff, investigators, and sponsors of clinical trials must read and understand the proposed rule, which has approximately 14,000 words. Based on HHS guidance on estimating this cost, we estimate that affected individuals will read the preamble and codified sections of the rule at a reading speed of approximately 200 to 250 words per minute, with an average

reading speed of 225 words per minute (= (200 + 250) / 2) (Ref. 1). We estimate that every member of a covered IRB and its legal staff would need to learn the requirements of the proposed rule. We use the constituent members of an IRB to represent an institution in this analysis. We estimate that all investigators for new clinical trials and the sponsors of clinical trials would also need to learn the requirements of the proposed rule.

We estimate that a representative IRB is composed of 8 individuals: 1 IRB administrator, 1 IRB chair, 1 IRB staff, and 10 voting members. We expect that the number of voting members may vary and estimate a lower bound of 5 members and an upper bound of 20 members. We also estimate that an IRB has an associated legal staff. We draw from Bureau of Labor Statistics (BLS) data used in the economic analysis of impacts of the revised Common Rule to estimate hourly wage rates for IRB members in 2018 dollars (Ref. 2). We use the wages of postsecondary education administrators to proxy for wages of an IRB administrator (Ref. 3), wages of postsecondary health teachers to proxy for wages of IRB chairs and IRB voting members (Ref. 4), wages of office and administrative support workers to proxy for wages of IRB administrative staff (Ref. 5), and wages of lawyers to proxy for wages of IRB legal staff (Ref. 6). We double each BLS wage rate to account for benefits and other indirect costs, yielding fully loaded hourly wages of $106.94 for IRB administrators (= $53.47 x 2), $117.62 for IRB chairs and voting members (= $58.81 x 2), $37.50 for IRB administrative staff (= $18.75 x 2), and $138.68 for legal staff (= $69.34 x 2). Table 2 presents a summary of the total hourly costs of IRB meetings. We estimate that the total hourly cost per IRB meeting is approximately $1,577, with a lower bound of approximately $988.81 and an upper bound

of approximately $2,753. While we have included legal staff in this summary table, we acknowledge that legal staff may not necessarily be present in IRB meetings; this one-hour contribution to the total meeting cost proxies for legal staff associated with an IRB.

Table 2. Summary of Hourly Costs per IRB Meeting Member and Legal Staff, 2018$			
IRB Member	Adjusted Wage	Members Per Meeting	Wage Per Meeting
Administrator	$106.94	1	$106.94
Chair	$117.62	1	$117.62
Voting Member (Primary)	$117.62	10	$1,1,76.15
Voting Member (Low)	$117.62	5	$588.08
Voting Member (High)	$117.62	20	$2,753.04
Administrative Staff	$37.50	1	$37.50
Legal Staff	$138.68	1	$138.68
Total Hourly Cost per IRB Meeting (Primary)			**$1,576.89**
Total Hourly Cost per IRB Meeting (Low)			**$988.81**
Total Hourly Cost per IRB Meeting (High)			**$2,753.04**

We also draw on BLS wage data to estimate hourly wage rates for investigators and the employees of sponsors of clinical trials. We use the wages of physicians and surgeons to proxy for the wages of investigators (Ref. 7) and the wages of physicians and lawyers to proxy for the employees of sponsors that would need to understand the rule. We request comment on these estimates.

We estimate that IRBs, investigators, and sponsors of clinical trials will incur one-time costs of learning the proposed rule. We estimate that there are 2,442 active IRBs regulated by both HHS and FDA, and 78 IRBs regulated exclusively by FDA, yielding 2,520 (= 2,442 + 78) IRBs affected by the proposed rule (Ref. 8). We estimate that each member of an IRB and its legal staff will read the rule at an hourly cost of approximately $1,577, with a lower bound of approximately $988.81 and an upper bound of

approximately $2,753, and that the rule is comprised of approximately 14,000 words. Based on an average reading speed of approximately 225 words per minute, with a lower bound of 250 words per minute and an upper bound of 200 words per minute, it will take the average reader approximately 1.04 hours to read the rule, with a lower bound of 0.93 hours and an upper bound of 1.17 hours. We multiply the number of IRBs by the hourly wage rate of IRB members and legal staff and the hours to read the rule to yield the cost of learning the rule to IRBs. We estimate that the total cost to IRBs of learning the proposed rule is approximately $4.1 million (= 2,520 x $1,576.89 x 1.04) in 2018 dollars, with a lower bound of approximately $2.3 million (= 2,520 x $988.81 x 0.93) and an upper bound of approximately $8.1 million (= 2,520 x $2,753.04 x 1.17).

We expect that the investigators for each affected clinical investigation will read the proposed rule, and that there are approximately 4,122 new clinical investigations per year that would be affected by the proposed rule (Ref. 9). We estimate that there are approximately 2 investigators associated with a clinical investigation, with a lower bound of 1 investigator and an upper bound of 4 investigators. We multiply the number of new clinical trials per year by the number of investigators per trial, the hourly wage of investigators, and the estimated hours to read the rule to yield the cost of learning the rule to investigators. We estimate that the total cost to investigators of learning the rule is approximately $1.7 million (= 4,122 x 2 x $202.86 x 1.04) in 2018 dollars, with a lower bound of approximately $0.8 million (= 4,122 x 1 x $202.86 x 0.93) and an upper bound of approximately $3.9 million (= 4,122 x 4 x $202.86 x 1.17).

Finally, we expect that the sponsors of clinical investigations will read the rule. We estimate that the number of affected sponsors is equal to the number of new clinical

investigations per year, and that each sponsor will employ physicians and lawyers to read the rule. We estimate that approximately 2 sponsor physicians and 2 sponsor lawyers will read the rule, with a lower bound of approximately 1 physician and 1 lawyer and an upper bound of 4 physicians and 4 lawyers. We request comment on these estimates. We multiply the number of physicians and lawyers by the hourly wages of physicians and lawyers and multiply this total hourly wage rate by the number of new clinical investigations per year and the estimated hours to read the rule, yielding the cost to sponsors of learning the rule. We estimate that the total cost to sponsors of learning the rule is approximately $2.9 million (= ((2 x $202.86) + (2 x $138.68)) x 4,122 x 1.04) in 2018 dollars, with a lower bound of approximately $1.3 million (= ((1 x $202.86) + (1 x $138.68)) x 4,122 x 0.93) and an upper bound of approximately $6.6 million (= ((4 x $202.86) + (4 x $138.68)) x 4,122 x 1.17).

We acknowledge that because some provisions of the proposed rule, such as the provisions eliminating the requirement to conduct continuing review of certain research, would affect some ongoing clinical trials, it is possible that more sponsors and investigators may be involved than we estimate here. However, as explained in the preamble to the proposed rule, FDA does not anticipate that investigators will revise informed consent forms and processes for ongoing clinical trials that are approved by an IRB before the proposed effective date of the rule. We, therefore, estimate that investigators conducting ongoing trials and sponsors of ongoing trials would most likely learn only about the provisions that would eliminate the requirement to conduct continuing review of some research and the corresponding revisions to requirements for progress reports in the IDE regulations. We estimate that the time to learn about these

provisions of the proposed rule, which would only affect some ongoing clinical trials, would be negligible. Therefore, we present this estimate and request comment on it. The total estimated cost to all affected entities of learning the rule is approximately $8.8 million (= $4.1 million + $1.7 million + $2.9 million) in 2018 dollars, with a lower bound of approximately $4.4 million (= $2.3 million + $0.8 million + $1.3 million) and an upper bound of approximately $18.6 million (= $8.1 million + $3.9 million + $6.6 million). Table 3 presents the estimated costs of learning the proposed rule.

Table 3. Costs to IRBs, Investigators, and Sponsors of Learning the Rule, 2018$			
	Primary	Low	High
Costs to IRBs			
Number of IRBs	2,520	2,520	2,520
Hourly wage rate of IRB members and legal staff	$1,576.89	$988.81	$2,753.04
Approximate number of words in rule	14,000	14,000	14,000
Number of words read per minute	225	250	200
Hours to read rule	1.04	0.93	1.17
Total costs to IRBs of learning the rule	**$4,120,937**	**$2,325,687**	**$8,093,947**
Costs to Investigators			
Number of new clinical investigations per year	4,122	4,122	4,122
Number of investigators per trial	2	1	4
Hourly wage rate of investigators	$202.86	$202.86	$202.86
Approximate number of words in rule	14,000	14,000	14,000
Number of words read per minute	225	250	200
Hours to read rule	1.04	0.93	1.17
Total costs to investigators of learning the rule	**$1,734,318**	**$780,443**	**$3,902,215**
Costs to Sponsors of Trials			
Number of new clinical trials per year	4,122	4,122	4,122
Number of sponsor physicians per trial	2	1	4
Number of sponsor lawyers per trial	2	1	4
Hourly wage rate of physicians	$202.86	$202.86	$202.86
Hourly wage rate of lawyers	$138.68	$138.68	$138.68
Approximate number of words in rule	14,000	14,000	14,000
Number of words read per minute	225	250	200
Hours to read rule	1.04	0.93	1.17
Total costs to sponsors of learning the rule	**$2,919,939**	**$1,313,973**	**$6,569,863**

Total costs of learning the rule	**$8,775,194**	**$4,420,102**	**$18,566,025**

2. Developing Informed Consent Forms

If finalized, the proposed rule will require the investigators for affected clinical trials to implement the new requirements that would modify the content, organization, and presentation of information of informed consent forms to facilitate a prospective subject's decision on whether to participate in research. These provisions will benefit potential human subjects by providing clearer, more comprehensive information about clinical investigations. If the rule is finalized, we expect that investigators will incur higher initial costs related to learning the revised requirements and implementing the new informed consent provisions, but that these costs will decrease in subsequent years as investigators become more familiar with the new provisions and informed consent templates used by some institutions are updated.

We estimate that investigators will incur costs related to developing informed consent forms that are in compliance with the new requirements. We estimate that the time burden associated with developing informed consent forms will be greatest in the first year after the proposed rule, if finalized, becomes effective. In subsequent years, we estimate that this burden will decrease as investigators become familiar with the rule and are able to draft forms in less time. We estimate that there are 4,122 new clinical trials per year and that each has an associated consent form that is developed by 1 investigator. We request comment on these estimates. We use the fully loaded hourly wages of physicians ($202.86) to proxy for the wages of investigators and estimate that, to comply with the new requirements in the proposed rule, it will take investigators approximately 0.5 hours longer than it currently takes to develop informed consent forms, with a lower

bound of approximately 0.25 hours and an upper bound of approximately 1 hour. We multiply the wage rate of physicians by the time burden of developing informed consent forms and multiply this total by the number of new clinical trials per year and the number of consents per trial to yield the costs to investigators of developing informed consent forms associated with this proposed rule. We estimate that the total cost to investigators of developing informed consent forms is approximately $418.1 thousand (= $202.86 x 0.5 x 4,122 x 1) in 2018 dollars, with a lower bound of approximately $209.0 thousand (= $202.86 x 0.25 x 4,122 x 1) and an upper bound of approximately $836.2 thousand (= $202.86 x 1 x 4,122 x 1). These estimates are summarized in Table 4.

Table 4. Costs to Investigators of Developing Informed Consent Forms, 2018$			
	Primary	Low	High
Number of new clinical trials per year	4,122	4,122	4,122
Number of consents per trial	1	1	1
Hourly wage rate of physicians	$202.86	$202.86	$202.86
Hours to develop informed consent forms	0.5	0.25	1
Total annual costs to investigators of developing informed consent forms	**$418,094**	**$209,047**	**$836,189**

We estimate that the time burden associated with the development of informed consent forms that comply with the proposed new requirements will decrease in the years after the proposed rule, if finalized, becomes effective, and that in the first year after the rule becomes effective, investigators will incur the full cost of development. In the following year, we expect that investigators will incur a reduced time burden as they become familiar with the provisions of the rule. In the third year after the rule becomes effective, we expect that investigators will experience a further reduced time burden that will remain constant in subsequent years. We estimate that in the first year after the rule is effective (Year 1), investigators will incur the full burden of informed consent form

development costs calculated above and reported in Table 5 (approximately $418.1 thousand in 2018 dollars, with a lower bound of approximately $209.0 thousand and an upper bound of approximately $836.2 thousand). In the following year (Year 2), we estimate that investigators will incur approximately 75 percent of these costs, or approximately $313.6 thousand (= $418.1 thousand x 0.75), with a lower bound of approximately $156.8 thousand (= $209.0 thousand x 0.75) and an upper bound of $627.1 thousand (= $836.2 thousand x 0.75). In Year 3 and in subsequent years, we estimate that investigators will incur approximately 50 percent of these costs, or approximately $209.0 thousand (= $418.1 thousand x 0.5), with a lower bound of approximately $104.5 thousand (= $209.0 thousand x 0.5) and an upper bound of approximately $418.1 thousand (= $836.2 x 0.5). The annualized costs of developing informed consent forms are approximately $244.4 thousand per year at a 3 percent discount rate over 10 years, with a lower bound of approximately $122.2 thousand and an upper bound of approximately $488.8 thousand. At a 7 percent discount rate, annualized costs are approximately $249.9 thousand, with a lower bound of approximately $124.9 thousand and an upper bound of approximately $499.7 thousand. We request comment on these estimates, particularly regarding our estimates of decreasing costs over time.

Table 5. Ten-Year Stream of Informed Consent Form Development Costs, thousands 2018$

Year	Primary	Low	High
Year 1	$418.1	$209.0	$836.2
Year 2	$313.6	$156.8	$627.1
Year 3	$209.0	$104.5	$418.1
Year 4	$209.0	$104.5	$418.1
Year 5	$209.0	$104.5	$418.1
Year 6	$209.0	$104.5	$418.1
Year 7	$209.0	$104.5	$418.1
Year 8	$209.0	$104.5	$418.1
Year 9	$209.0	$104.5	$418.1

Year 10	$209.0	$104.5	$418.1
Annualized Costs (3%)	**$244.4**	**$122.2**	**$488.8**
Annualized Costs (7%)	**$249.9**	**$124.9**	**$499.7**

3. Recordkeeping Related to Continuing Review

If finalized, the proposed rule will revise the IRB recordkeeping requirements for certain determinations related to the need for continuing review of clinical investigations. Specifically, IRBs would be required to retain records of the rationale for conducting continuing review of research that otherwise would no longer require continuing review under proposed § 56.109(g). We expect that a proportion of IRBs will incur costs from new recordkeeping requirements for certain determinations related to the need for continuing review.

Based on discussion with FDA subject matter experts, we estimate that IRBs will decide to conduct approximately 500 continuing reviews that otherwise would not be required under proposed § 56.109(g) and will, therefore, incur costs related to the new recordkeeping requirements, with a lower bound of approximately 250 IRB continuing reviews and an upper bound of approximately 1,000 IRB continuing reviews. We estimate that each IRB employs a recordkeeper and use the fully loaded wage of office and administrative support workers to proxy for the wages of IRB recordkeepers. The estimated time burden of fulfilling these new requirements is approximately 0.5 hours, with a lower bound of approximately 0.25 hours and an upper bound of approximately 1 hour. We multiply the number of affected IRB reviews by the number of recordkeepers, the wage of recordkeepers, and the time burden of the new requirements to yield the total annual costs of the new recordkeeping requirements. We estimate that the total annual cost of the new recordkeeping requirements is approximately $9,375 (= 500 x 1 x $37.50

x 0.5) in 2018 dollars, with a lower bound of approximately $2,344 (= 250 x 1 x $37.50 x 0.25) and an upper bound of approximately $37,500 (= 1,000 x 1 x $37.50 x 1). These estimates are summarized in Table 6.

Table 6. Costs of New Recordkeeping Requirements, 2018$			
	Primary	Low	High
Number of affected IRB reviews	500	250	1,000
Number of recordkeepers per IRB	1	1	1
Hourly wage of IRB recordkeepers	$37.50	$37.50	$37.50
Hours to fulfill new recordkeeping requirements	0.5	0.25	1
Total annual costs of new recordkeeping requirements	**$9,375**	**$2,344**	**$37,500**

The estimated costs of the proposed rule are summarized in Table 7.

Table 7. Summary of Costs of the Proposed Rule, 2018$			
	Primary	Low	High
Cost of learning the rule (one-time)	$8,775,194	$4,420,102	$18,566,025
Costs to investigators of developing informed consent forms (annualized, 3%)	$244,390	$122,195	$488,780
Costs to investigators of developing informed consent forms (annualized, 7%)	$249,862	$124,931	$499,724
Annual cost of new recordkeeping requirements	$9,375	$2,344	$37,500
Total costs of the proposed rule (annualized, 3%)	**$9,028,959**	**$4,544,641**	**$19,092,305**
Total costs of the proposed rule (annualized, 7%)	**$9,034,431**	**$4,547,377**	**$19,103,249**

E. Cost Savings of the Proposed Rule

If finalized, we estimate that the proposed rule will benefit affected entities in the form of cost savings related to (1) the harmonization of informed consent requirements with those of the revised Common Rule; and (2) the elimination of continuing review for some clinical investigations.

1. Reviewing Informed Consent Forms

We estimate that IRBs that review clinical trials that are regulated by both FDA and the HHS Office for Human Research Protections (OHRP) will benefit from the harmonization of requirements for FDA-regulated clinical investigations with the revised Common Rule. We estimate that these benefits will take the form of cost savings stemming from the reduced time burden of reviewing informed consent forms.

We estimate that there are 2,442 active IRBs that are regulated by both FDA and OHRP [Ref. 8] that will benefit from harmonization of these requirements, and that the hourly wage rate of all IRB members and associated legal staff is approximately $988.81. We estimate that the reduced time burden generated by harmonization of FDA's informed consent requirements with the revised Common Rule is approximately 0.5 hours, with a lower bound of 0.25 hours and an upper bound of 1 hour, and request comment on this estimate. We multiply the number of IRBs, the hourly wage rate of IRB members and legal staff, and the estimated reduced time burden of harmonization to yield the cost savings of informed consent form review to IRBs. We estimate that the annual cost savings to IRBs of reviewing informed consent forms is approximately $1.9 million (= 2,442 x $1,577 x 0.5), with a lower bound of approximately $0.6 million (= 2,442 x $988.81 x 0.25) and an upper bound of approximately $6.7 million (= 2,442 x $$2,753 x 1). These estimates are summarized in Table 8.

Table 8. Cost Savings of IRBs Reviewing Informed Consent Forms

	Primary	Low	High
Number of IRBs	2,442	2,442	2,442
Hourly wage rate of IRB members and legal staff	$1,576.89	$988.81	$2,753.04
Reduced time burden of informed consent harmonization (hours)	0.5	0.25	1
Annual cost savings to IRBs of reviewing informed consent forms	**$1,925,382**	**$603,670**	**$6,722,931**

2. Elimination of Continuing Review Under Certain Circumstances

If finalized, the proposed rule would allow IRBs to eliminate continuing review of research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study: (1) data analysis, including analysis of identifiable private information or identifiable biospecimens; or (2) accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care. We expect that this provision will generate cost savings for IRBs that will be able to forgo continuing review for a significant number of clinical investigations in harmonization with a similar provision in the revised Common Rule.

To estimate the number of trials that may be subject to annual IRB continuing review under 21 CFR 56.109(f) and the number of investigational sites for those trials, we conducted a search of ClinicalTrials.gov (https://clinicaltrials.gov/) for active, ongoing, U.S. interventional trials [Ref. 9]. We estimate this number to be 28,707 trials conducted at 277,760 investigational sites. Using these estimates, we estimate the number of trials and sites that would meet the criteria under proposed § 56.109(g) to eliminate continuing review to be 6,715 trials at 80,749 sites. Due to limitations in the available information used for these estimates, we assume that, for multisite clinical trials, each site's IRB would conduct continuing review of the trial. However, we recognize that this could lead to an overestimate in the number of continuing reviews for multisite studies that use a single IRB review model. We estimate that IRBs would conduct 500 continuing reviews of research that otherwise would not require continuing review under proposed 21 CFR 56.109(g). Thus, we estimate that 80,249 IRB continuing reviews would be eliminated (80,749 - 500 = 80,249). We estimate that the hourly wage rate of all

IRB members is approximately $850.13 and that the reduced time burden of this provision is approximately 1 hour per IRB continuing review, with a lower bound of 0.5 hours and an upper bound of 2 hours. We request comment on this estimate. We multiply the number of continuing reviews, the hourly wage rate of IRB members, and the reduced time burden to yield the cost savings of eliminating continuing review to all IRBs. We estimate that the annual cost savings to IRBs of eliminating continuing review is approximately $115.4 million (= 80,249 x $1,438.21 x 1) in 2018 dollars, with a lower bound of approximately $34.1 million (= 80,249 x $850.13 x 0.5) and an upper bound of approximately $419.6 million (= 80,249 x $2,6414.36 x 2).

Finally, we estimate that for each site with an active, ongoing clinical investigation that would meet the criteria for elimination of continuing review, there are sponsors or investigators that will benefit from the elimination of continuing review in the form of reduced time burdens preparing annual and/or progress reports for submission to the IRB. We estimate that the number of affected sponsors or investigators is equal to the number of continuing reviews eliminated per year, and that each sponsor or investigator will experience a reduced time burden of approximately 1 hour, with a lower bound of approximately 1 hour and an upper bound of approximately 2 hours. We use the fully loaded hourly wages of physicians ($202.86) to proxy for the wages of sponsors and investigators and multiply the number of such physicians by the physician wage rate by the number of continuing reviews eliminated and the estimated reduced time burden to yield the cost savings of the elimination of continuing review to sponsors or investigators. We estimate that the annual cost savings to sponsors or investigators of eliminating continuing review is approximately $16.3 million (= 80,249 x 1 x $202.86 x 1) in 2018

dollars, with a lower bound of approximately $8.1 million (= 80,249x 1 x $202.86 x 0.5) and an upper bound of approximately $65.1 million (= 80,249 x 2 x $202.86 x 2).

We recognize that IRBs may choose to conduct more continuing reviews that might otherwise be eliminated than we estimate. Further, some new and ongoing clinical investigations will progress to a point that continuing review is no longer required under proposed § 56.109(g) over time. We do not have sufficient data on the rates and timing of when trials become eligible to eliminate continuing review under the provisions of the proposed rule, and request comment on these topics. We estimate that in the first year after the proposed rule, if finalized, becomes effective, approximately 50 percent of IRBs and trials will receive cost savings from this provision, We estimate that the total annual cost savings of the elimination of continuing review is approximately $65.8 million (= 0.5 x ($115.4 million + $16.3 million)) in 2018 dollars, with a lower bound of approximately $21.1 million (= 0.5 x ($34.1 million + $8.1 million)) and an upper bound of approximately $242.4 million (= 0.5 x ($419.6 million + $65.1 million)). These estimates are summarized in Table 10.

Table 10. Cost Savings of Eliminating Continuing Review			
	Primary	Low	High
Cost Savings to IRBs			
Number of trial sites*	80,249	80,249	80,249
Hourly wage rate of IRB members	$1,438.21	$850.13	$2,614.36
Reduced hourly time burden of eliminating continuing review per site	1	0.5	2
Cost savings to IRBs of eliminating continuing review	**$115,414,853**	**$34,111,134**	**$419,600,045**
Cost Savings to Sponsors or Investigators			
Number of trial sites*	80,249	80,249	80,249
Number of sponsor or investigator physicians	1	1	2
Hourly wage rate of physicians	$202.86	$202.86	$202.86

Reduced hourly time burden of eliminating continuing review per trial site	1	0.5	2
Cost savings to sponsors or investigators of eliminating continuing review	**$16,279,312**	**$8,139,656**	**$65,117,249**
Percent of IRBs that will continue to conduct continuing review	50	50	50
Total annual cost savings of eliminating continuing review	**$65,847,082**	**$21,125,395**	**$242,358,647**

*Number of ongoing, active trial sites that meet criteria for eliminating continuing review

The total estimated annualized cost savings of the proposed rule are approximately $67.7 million (= $1.9 million + $65.8 million) in 2018 dollars, with a lower bound of approximately $21.7 million (= $0.6 million + $21.1 million) and an upper bound of approximately $249.1 million (= $6.7 million + $242.4 million). These estimates are summarized in Table 12.

Table 12. Summary of Cost Savings of the Proposed Rule, millions 2018$			
	Primary	Low	High
Annual cost savings of developing informed consent forms	$1.9	$0.6	$6.7
Annual cost savings of eliminating continuing review	$65.8	$21.1	$242.4
Total annual cost savings of the proposed rule	**$67.7**	**$21.7**	**$249.1**

Finally, we subtract estimated total cost savings from total costs to yield the net costs of the proposed rule. We estimate that the net costs of the proposed rule are approximately ($58.6) million (= $8.8 million - $1.5 million - $65.8 million + $9,375) in 2018 dollars at a 3 percent discount rate, with a lower bound of approximately ($17.1) million (= $4.4 million - $0.4 million - $21.1 million + $2,344) and an upper bound of approximately ($229.6) million (= $18.6 million - $5.9 million - $242.4 million +

$37,500). At a 7 percent discount rate, the net costs of the proposed rule are approximately ($58.6) million (= $8.8 million - $1.5 million - $65.8 million + $9,375), with a lower bound approximately ($17.1) million (= $4.4 million - $0.4 million - $21.1 million + $2,344) and an upper bound of approximately ($229.6) million (= $18.6 million - $5.8 million - $242.4 million + $37,500).

We present these negative net costs as positive cost savings and estimate that their 10-year present value is approximately $567.4 million in 2018 dollars, with a lower bound of approximately $180.0 and an upper bound of approximately $2,102.2 million, discounted at 3 percent. Discounted at 7 percent, the estimated present value of net cost savings is approximately $466.0 million, with a lower bound of approximately $147.6 and an upper bound of approximately $1,728.3 million. The annualized estimated net cost savings of the proposed rule are approximately $66.5 million in 2018 dollars, with a lower bound of approximately $21.1 million and an upper bound of approximately $246.4 million, discounted at 3 percent over 10 years. When discounted at 7 percent, the annualized estimated net cost savings of the proposed rule are approximately $66.3 million, with a lower bound of approximately $21.0 million and an upper bound of approximately $246.1 million. These estimates are summarized in Table 13.

Table 13. Net Costs of the Proposed Rule, millions 2018$

	Primary	Low	High
Learning the proposed rule	$8.8	$4.4	$18.6
Developing informed consent forms (3%)	($1.5)	($0.4)	($5.9)
Developing informed consent forms (7%)	($1.5)	($0.4)	($5.9)
Eliminating continuing review (3%)	($65.8)	($21.1)	($242.4)
Eliminating continuing review (7%)	($65.8)	($21.1)	($242.4)
New recordkeeping requirements (thousands$)	$9,375	$2,344	$37,500
Net costs of the proposed rule (3%)	**($58.6)**	**($17.1)**	**($229.6)**
Net costs of the proposed rule (7%)	**($58.6)**	**($17.1)**	**($229.6)**
Present value of net cost savings (3%)	$567.4	$180.0	$2,102.2
Present value of net cost savings (7%)	$466.0	$147.6	$1,728.3

Annualized net cost savings (3%)	**$66.5**	**$21.1**	**$246.4**
Annualized net cost savings (7%)	**$66.3**	**$21.0**	**$246.1**

3. Non-Quantified Benefits

If finalized, the proposed rule may also have benefits that we cannot quantify due to data limitations. We expect that these benefits include increased efficiency of clinical trials and FDA-regulated medical product development and improved human subject knowledge by providing subjects with clearer information regarding clinical trials. Finally, we expect that the proposed technical and editorial changes to FDA regulations will increase clarity without compromising the safety and protection of human subjects.

F. Distributional Effects

We estimate that the proposed rule, if finalized, would not have significant distributional effects. We expect that because the procedural changes in the proposed rule do not vary by the size of affected entities, and that the estimated costs and cost savings would be proportionally incurred by covered IRBs, investigators, and sponsors.

G. International Effects

We estimate that the proposed rule, if finalized, would apply to FDA-regulated research conducted by domestic sponsors both in and outside of the United States. We estimate that foreign sponsors of FDA-regulated research may benefit from cost savings, but we lack sufficient data to estimate the number of foreign sponsors that may be affected by the proposed rule. The rule, if finalized, would not adversely affect foreign sponsors' ability to conduct FDA-regulated research and would potentially facilitate foreign investment in domestic medical product research.

H. Uncertainty and Sensitivity Analysis

We have identified several sources of uncertainty in our analysis of economic impacts. Specifically, we lack sufficient data on the number of investigators per clinical trial, the number of sponsor physicians per clinical trial, the number of sponsor lawyers per trial, the time burden of developing informed consent forms for investigators, the reduced time burden associated with harmonization of informed consent requirements for IRBs, investigators, and sponsors, the number of hours of continuing review per IRB, the time burden and number of IRBs affected by the proposed recordkeeping provisions, and the total number of new records generated from the proposed recordkeeping provisions. Throughout our analysis, we have estimated ranges of likely values for these variables to represent this uncertainty. Additionally, we have performed Monte Carlo simulation analysis of the net cost savings of the proposed rule at the 5th and 95th percentile of likelihood. We estimate that the present value of net cost savings ranges from approximately $493.8 million to approximately $615.6 million, discounted at 3 percent. When discounted at 7 percent, the present value of cost savings ranges from approximately $415.9 million to approximately $515.8 million. The annualized cost savings of the proposed rule range from approximately $57.6 million to $71.9 million, discounted at 3 percent. When discounted at 7 percent, the annualized cost savings of the proposed rule range from approximately $59.2 million to approximately $73.4 million. The results of our uncertainty and sensitivity analysis are summarized in Table 14.

Table 14. Simulation Results at 5th and 95th Percentile, millions 2018$			
	Primary	5th Percentile	95th Percentile
Present value of net cost savings (3%)	$567.4	$615.6	$493.8
Present value of net cost savings (7%)	$466.0	$515.8	$415.9
Annualized net cost savings (3%)	**$66.5**	**$71.9**	**$57.6**
Annualized net cost savings (7%)	**$66.3**	**$73.4**	**$59.2**

I. Analysis of Regulatory Alternatives to the Proposed Rule

We have identified and assessed one regulatory alternative to the proposed rule. Under this alternative regulatory option, the proposed rule would not propose revisions to the requirements for the content of informed consent documents. This option would reduce the time burden associated with developing informed consent documents and the cost savings of harmonization for IRBs. This regulatory alternative would reduce the estimated net cost savings of the proposed rule and would forgo the benefits of increased efficiency in medical product innovation. Under this alternative regulatory option, the total annualized net cost savings of the proposed rule would be approximately $64.8 million in 2018 dollars, with a lower bound of approximately $20.6 million and an upper bound of approximately $240.2 million, discounted at 3 percent. When discounted at 7 percent, the total annualized net costs savings of the proposed rule would be approximately $64.7 million, with a lower bound of approximately $20.5 million and an upper bound of approximately $239.9 million. A summary of our analysis of regulatory alternatives is presented in Table 15.

Table 15. Cost Savings of the Proposed Regulatory Alternative, millions 2018$			
	Primary	Low	High
Annualized net cost savings (3%)	$64.8	$20.6	$240.2
Annualized net cost savings (7%)	$64.7	$20.5	$239.9

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. If finalized, the small entities that would most likely be affected by the proposed rule are sponsors of

drug and medical device research and medical institutions, primarily medical and surgical hospitals that are affiliated with affected IRBs. Because estimated cost savings of the proposed rule are greater in magnitude than estimated costs, and because we do not expect the effects of the rule to affect entities by size, 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.

For this analysis, the small entities that are 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 hospitals, we use Census Bureau data with the NAICS code 622110 (Ref. 10), and the Small Business Administration definition for a small hospital of $38.5 million in annual revenues (Ref. 11). Based on SBA revenue threshold, 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 estimate that 42 percent, or approximately 1,058 of IRBs covered by the proposed rule are affiliated with small entities (= 0.42 x 2,520) and that 42 percent of the estimated costs and cost savings of the proposed rule will be incurred by small entity IRBs. We divide the net cost savings of the proposed rule for small entities by the

number of small entities to yield per IRB cost savings of approximately $24,407 (= $66.5 million x 0.42 / 1,058), with a lower bound of approximately $ 8,377 (= $21.1 million x 0.42 / 1,058) and an upper bound of approximately $97,831 (= $246.4 million x 0.42 / 1,058), discounted at 3 percent. At a 7 percent discount rate, the estimated cost savings per small entity IRB are approximately $26,338 (= $66.3 million x 0.42 / 1,058), with a lower bound of approximately $8,342 (= $21.0 million x 0.42 / 1,058) and an upper bound of approximately $97,685 (= $246.1 million x 0.42 / 1,058). Because we estimate that cost savings exceed costs, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. Because of the lack of high quality, comprehensive data on IRBs, particularly with regard to the revenues of associated medical institutions by which SBA defines entities as small and very small businesses, we are unable to definitively estimate the burden of the proposed rule on small entities. We request comment on whether such data are available.

We also estimate that small firms that sponsor medical product research will be affected by the proposed rule. Due to data limitations, the main Economic Analysis of Impacts uses the estimated number of new affected trials to measure the effect of the proposed rule on sponsors; this data does not allow us to examine the number of trials associated with different product classes. For example, some affected industries (such as medical devices) may have a higher proportion of small firms than others (such as drugs). Because of these possible differences in industry makeup and our limited data, we cannot estimate the effect of the proposed rule on small firms that sponsor medical product research with accuracy. We do, however, expect that affected entities will experience cost

savings and will not incur significant costs. We request comment on the makeup of affected industries by firm size.

IV. References

The following references are on display at 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, 240-402-7500; they are also available electronically at http://www.regulations.gov. We have verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Department of Health and Human Services, "Guidelines for Regulatory Impact Analysis,"2016, available at: https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis, accessed November 26, 2021.

2. "Federal Policy for the Protection of Human Subjects", 82 Fed. Reg. 7149 (January 19, 2017), available at https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf, accessed March 5, 2018.

3. Bureau of Labor Statistics, "Occupation Employment and Wages, May 2018, 11-9033 Education Administrators, Postsecondary," available at: https://www.bls.gov/oes/current/oes119033.htm, accessed July 12, 2019.

4. Bureau of Labor Statistics, "Occupational Employment and Wages, May 2018, 25-1071 Health Specialties Teachers, Postsecondary," available at: https://www.bls.gov/oes/current/oes251071.htm, accessed July 12, 2019.

5. Bureau of Labor Statistics, "Occupational Employment and Wages, May 2018, 43-0000 Office and Administrative Support Occupations (Major Group)," available at: https://www.bls.gov/oes/current/oes430000.htm, accessed July 12, 2019.

6. Bureau of Labor Statistics, "Occupational Employment and Wages, May 2018, 23-1011 Lawyers," available at: https://www.bls.gov/oes/current/oes231011.htm, accessed July 12, 2019.

7. Bureau of Labor Statistics, "May 2018 National Occupational Employment and Wage Estimate United States: 29-1060 Physicians and Surgeons," available at: https://www.bls.gov/oes/current/oes_nat.htm, accessed July 12, 2019.

8. Memorandum to File, FDA summary of data analysis; HHS, "Office for Human Research Protections (OHRP) Database for Registered IORGs & IRBs, Approved FWAs, and Documents Received in Last 60 Days," prepared by Christian Brown, FDA, March 28, 2019.

9. Memorandum to File, FDA summary of data analysis and staff meeting on "Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards" proposed rule, prepared by Christian Brown, FDA, June 5, 2020.

10. North American Industry Classification System (NAICS), U.S. Census Bureau, "General Medical and Surgical Hospitals NAICs Code 622110" available at: https://www.census.gov/naics/?input=622110&year=2017&details=622110, accessed June 2, 2022.

11. U.S. Small Business Administration, "Table of Small Business Size Standards Matched to North American Industry Classification System Codes," https://www.sba.gov/sites/default/files/files/Size_Standards_Table.pdf, accessed July 12, 2019.