DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations

Docket No. FDA-2018-N-2727

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104-121), 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, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). Rules are significant under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of the Office of Information and Regulatory Affairs [OIRA] for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this final rule is not a significant regulatory action under Section 3(f)(1).

A rule is "major" under the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act if it has resulted or is likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act. OIRA has determined that this final rule is not a major rule under the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule is unlikely to impose a substantial burden on the affected small entities, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

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 issuing "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 $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Changes Made to the Preliminary Regulatory Impact Analysis

The final rule allows an Institutional Review Board (IRB) responsible for the review, approval, and continuing review of clinical investigations to approve an informed consent procedure that does not include or that alters certain informed consent elements, or to waive the requirement to obtain informed consent, for certain minimal risk clinical investigations if the IRB finds and documents five criteria. The proposed rule's economic analysis of impacts did not anticipate additional costs associated with this rulemaking and estimated small cost savings associated with harmonization of FDA's informed consent regulations with the analogous provision for waiver or alteration of informed consent for certain minimal risk research under the Federal Policy for the Protection of Human Subjects (codified by the Department of Health and Human Services (HHS) at 45 CFR part 46,

subpart A, and generally referred to as the Common Rule). (See 83 FR 57378, 57383-57384, November 15, 2018). As the proposed rule was deemed not significant, that analysis was not submitted to OIRA for review under E.O. 12866. Of the 46 public comments received on the proposed rule, none commented directly on the economic analysis of impacts (FDA responds to the comments received in the preamble to the final rule). However, as part of developing a response to one public comment requesting an additional description of the potential drawbacks of the rule, we reconsidered potential costs and reviewed the steps that the affected entities will need to take to request or review a waiver or alteration of consent as permitted by this rule. We identify one-time costs associated with reading and implementing the rule and annual costs associated with drafting and reviewing requests for a waiver or alteration of informed consent under the final rule. We include a revised analysis of costs and cost savings in the Economic Analysis of Impacts (see Sections E-G on the revised costs and costs savings analysis).

Additionally, the proposed rule put forward four criteria that an IRB would have to find and document to grant a waiver or alteration of informed consent and sought public comment on whether to include a fifth criterion that is included in the Common Rule. Based on public comment, the final rule adopts the fifth criterion and harmonizes with the Common Rule's provision for waiver or alteration of consent for minimal risk research at 45 CFR 46.116(f). We do not expect that this additional criterion contributes significantly to the overall costs of the final rule (see section D – Costs of the Rule). This expectation is based on our review of publicly available materials, such as information provided on IRB websites,[1] suggesting that a

[1] These include websites for IRBs at Washington State University (available at: https://irb.wsu.edu/irb-roster-member-responsibilities/), University of Iowa (available at: https://hso.research.uiowa.edu/become-irb-member). University of Nevada at Reno (available at: https://www.unr.edu/research-integrity/human-research/human-

total of 2-3 hours is needed for IRB review and discussion of a study (including study protocol, participant materials, etc.). We estimate that review and discussion of whether to approve a request for a waiver or alteration of consent for a study will take up to one hour total IRB review time, with that time including discrete discussion of each criterion, as well as consideration of the waiver as a whole. We consider the additional time to discuss this one waiver criterion, where applicable, to be small in comparison to the total time for the IRB to review and discuss the study. Accordingly, we estimate the overall added cost of the addition of the fifth criterion to be de minimis. Further, any added cost would be outweighed by the cost savings of harmonization between FDA regulations and the Common Rule's provision for waiver or alteration of informed consent for minimal risk research (see section E – Cost Savings of the Rule) and by the non-quantitative benefits in the form of healthcare advances stemming from FDA-regulated minimal risk clinical investigations that may now proceed using a waiver or alteration of informed consent under the final rule (see Section F – Non-quantified Benefits of the Rule).

C. Summary of Costs and Benefits

The rule does not require any IRB to waive or alter informed consent, nor does it require any person to request such a waiver or alteration. However, we expect costs in the form of affected IRBs, as well as investigators and sponsors of clinical investigations, reading and learning the rule. We also expect costs in the form of drafting new waiver or alteration requests, and additional recordkeeping burdens associated with reviewing and documenting IRB decisions on waiver or alteration requests. The net present value of the estimated costs of the rule are approximately $10.1 million, with a lower bound of approximately $8.1 million and an upper

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research-protection-policy-manual/630-irb-meetings), and University of Pittsburgh (available at: https://www.hrpo.pitt.edu/irb-community-member-frequently-asked-questions).

bound of approximately $14.0 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the estimated costs of the rule are approximately $9.1 million, with a lower bound of approximately $7.5 million and an upper bound of approximately $12.4 million. The estimated annualized costs of the rule are approximately $1.2 million, with a lower bound of approximately $0.9 million and an upper bound of approximately $1.6 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the estimated annualized costs of the rule are approximately $1.3 million, with a lower bound of approximately $1.1 million and an upper bound of approximately $1.8 million.

We expect that there will be cost savings from harmonization of FDA's informed consent regulations with the provision for waiver or alteration of informed consent for certain minimal risk research in the Common Rule. The estimated net present value of the cost savings of the rule are approximately $1.7 million, with a lower bound of approximately $0.9 million and an upper bound of approximately $3.5 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the estimated cost savings of the rule are approximately $1.4 million, with a lower bound of approximately $0.7 million and an upper bound of approximately $2.8 million. The estimated annualized cost savings of the rule are approximately $0.2 million, with a lower bound of approximately $0.1 million and an upper bound of approximately $0.4 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the estimated annualized costs savings of the rule are approximately $0.2 million, with a lower bound of approximately $0.1 million and an upper bound of approximately $0.4 million.

We also expect benefits in the form of healthcare advances from minimal risk clinical investigations for which the requirements for informed consent are waived or altered under the final rule. We cannot quantify all benefits because of the lack of relevant data available to FDA,

but these benefits are described in Section I.E of this analysis. The costs and cost savings of the rule are summarized in Table 1.

Table 1. Summary of Costs, Costs Savings, and Distributional Effects of the Proposed Rule (millions $)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Costs	Annualized Monetized millions/year							
	Annualized Quantified	$1.3	$1.1	$1.8	2020	7%	10 years	
		$1.2	$0.9	$1.6	2020	3%	10 years	
	Qualitative							
	Annualized Monetized millions/year							
	Annualized Quantified	$0.2	$0.1	$0.4	2020	7%	10 years	
		$0.2	$0.1	$0.4	2020	3%	10 years	
	Qualitative	Healthcare advances stemming from minimal risk clinical investigations that can proceed using a waiver or alteration of informed consent and that otherwise would not have been conducted.						
Transfers	Federal Annualized							
	Monetized $millions/year							
		From:			To:			
	Other Annualized							
	Monetized $millions/year							
		From:			To:			
Effects	State, Local or Tribal Government:							

D. Costs of the Rule

We anticipate that IRBs affected by this rule will incur costs associated with reading and learning the rule. We estimate that IRB members, clinical investigators, and sponsors of FDA-regulated clinical investigations will read the rule. To estimate the associated reading costs for

IRBs, we conducted a search for active IRBs regulated by both FDA and the HHS Office for Human Research Protections (OHRP) in the "Office for Human Research Protections (OHRP) Database for Registered IRB Organizations (IORGs) & IRBs, Approved Federalwide assurances (FWAs), and Documents Received in the Last 60 Days" (Ref. 1). Using these data, we estimate that there are 2,507 active IRBs regulated by both HHS and FDA, and 68 IRBs regulated exclusively by FDA, yielding 2,575 (= 2,507 + 68) IRBs affected by the rule. We estimate that all IRBs affected by this rule will incur a one-time cost in the form of time spent reading the rule. We estimate that IRB staff (including IRB administrators, chairs, 10 voting members, and administrative staff) will read the rule, and that the rule contains approximately 21,500 words. We follow HHS guidance on reading speed (Ref. 2) and estimate that affected individuals will read the rule at a speed of approximately 225 words per minute, the midpoint of 200 and 250 words per minute. The per hour reading speed is approximately 13,500 words (= 225 x 60), yielding a time burden of approximately 1.59 hours (= 21,500 / 13,500).

To evaluate associated costs for investigators and sponsors who will read and learn this rule in order to draft a waiver or alteration request, we estimated the number of studies that potentially qualify for a waiver or alteration of informed consent. For this estimate, we selected all studies from ClinicalTrials.gov registered as having started in calendar year 2021, applied exclusion parameters,[2] and ended with 2,201 studies from ClinicalTrials.gov that include those most likely to be minimal risk clinical investigations, but are not limited to such clinical investigations. For example, device studies reported on ClinicalTrials.gov as not having an IDE

[2] The estimated number of annual studies that may potentially be appropriate for a waiver or alteration of informed consent was estimated by identifying all studies on ClinicalTrials.gov that reported starting in the calendar year 2021, and excluding records for studies that were withdrawn prior to enrollment of any participants and records describing expanded access protocols. From the remaining studies (n= 32,893), we excluded records for studies conducted only at foreign sites (n= 22,624), records for trials conducted under and IND or IDE (n= 3,664), and trials not reporting inclusion of an FDA-regulated product (n= 4,404). These exclusions were intended to eliminate trials that were unlikely to be minimal risk or to fall under FDA's oversight (n = 2,201).

would likely include studies of "non-significant risk" devices that are conducted under the abbreviated IDE requirements.[3] As discussed in comment response 11 in the preamble to the final rule, "non-significant risk" and "minimal risk" are different concepts that serve different regulatory purposes, so "non-significant risk" device studies captured in our ClinicalTrials.gov sample may not meet the minimal risk criterion at § 50.22(a) for a waiver or alteration of consent. In addition, not all drug studies that are exempt from the requirement to have an IND would qualify as minimal risk. We therefore expect that the 2,201 studies identified includes studies that are more than minimal risk. They may also include studies that would not be FDA-regulated clinical investigations, as defined at 21 CFR 50.3(c).

In addition, to qualify for a waiver, the studies identified here would need to meet all the requirements outlined in § 50.22, not just the "minimal risk" criterion. Many of these potential minimal risk investigations may be practicable to conduct without a waiver or alteration of informed consent and thus investigators would be unlikely to request a waiver or alteration for those studies. Clinical investigators and IRBs have implemented FDA's general requirements for informed consent at Part 50 for decades; we do not expect clinical investigators to often propose, or for IRBs to often find, that it is impracticable to carry out a clinical investigation without a waiver or alteration of informed consent. Given these additional considerations, we estimate that, at most, an investigator might request a waiver or alteration of informed consent under new § 50.22 for approximately 25 percent, or 551, of the 2,201 investigations identified.[4]

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[3] See 21 CFR 812.2(b).

[4] FDA regulations have not previously provided for a waiver or alteration of informed consent for minimal risk research. Therefore, the clinical investigations that would have qualified for a waiver or alteration under new § 50.22 may not have proceeded in the past and may not all be captured in historical data. However, FDA issued a guidance in July 2017 stating that the agency does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described in the guidance (82 FR 34535). Thus, such studies may have been initiated in 2021 and submitted to ClinicalTrials.gov.

Our estimate of approximately 551 investigations is a conservative estimate of the number of requests that will be developed and reviewed for this type of FDA-regulated research.

For wage estimates, we draw from US Department of Labor, Bureau of Labor Statistics data to estimate hourly wage rates for IRB chairs, IRB voting members, and IRB administrative staff in 2020 dollars. Based on an economic analysis of impacts of revisions to the Common Rule (Ref. 3), we use wages for postsecondary education administrators to proxy for IRB administrator wages (Ref. 4), wages for office and administrative support workers to proxy for IRB administrative staff wages (Ref. 5), and wages for postsecondary health teachers (Ref. 6) to proxy for the wages of IRB chairs and IRB voting members. We double each hourly wage to account for benefits and overhead, yielding wage rates of $110.76 for IRB administrators (= $55.38 x 2), $40.76 for IRB administrative staff (= $20.38 x 2), $120.08 for IRB chairs (= $60.04 x 2), and $120.08 for IRB voting members (= $60.04 x 2). We estimate that the costs of reading the rule to IRBs are approximately $6.0 million (= 2,575 x 1.59 x ($110.76 + $120.08 + ($120.08 x 10) + $40.76)).

We use BLS hourly wage data for physicians and surgeons (Ref. 7), doubled for benefits and overhead (= $105.22 x 2) for the wage rate for clinical investigators. We estimate that each potential minimal risk clinical investigation will include 1 investigator, yielding a clinical investigator reading cost of approximately $184.7 thousand (= 551 x $210.44 x 1 x 1.59). We estimate the time burden of reading the rule associated with sponsors of clinical investigations will be incurred by 1 scientist; we use the mean hourly wage rate for life scientists (Ref. 8) with an hourly wage rate of approximately $88.62 (= $44.31 x 2). We multiply the number of potential minimal risk clinical investigations by these wage rates and the estimated time burden of reading to yield a sponsor reading cost of approximately $77.8 thousand (= 551 x $88.62 x 1 x

1.59). The total one-time cost of reading the rule to all affected entities is approximately $6.3 million (= $6.0 million + $184.7 thousand + $77.8 thousand).

The net present value of the estimated reading cost is approximately $6.1 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the net present value is approximately $5.9 million. The annualized cost of reading the rule is approximately $717.1 thousand at a 3 percent discount rate and approximately $838.4 thousand at a 7 percent discount rate. The estimated costs of reading the rule are summarized in Table 3.

Table 3. Costs of Reading the Rule (2020$)

Number of active IRBs regulated by FDA and OHRP or FDA only	2,575
Words read per minute	225
Words read per hour	13,500
Number of words in rule	21,500
Time burden of reading the rule (hours)	1.59
Hourly wage, IRB administrator	$110.76
Hourly wage, IRB administrative staff	$40.76
Hourly wage, IRB chair	$120.08
Hourly wage, IRB voting member (10 members per IRB)	$1,200.80
Total reading cost to IRBs (one-time)	$6,038,203
Number of potential clinical investigations	551
Number of investigators per clinical investigation	1
Hourly wage, investigators	$210.44
Time burden of reading the rule (hours)	1.59
Total reading cost to clinical investigators (one-time)	$184,665
Number of affected clinical investigation sponsors	551
Hourly wage, life scientists	$88.62
Time burden of reading the rule (hours)	1.59
Total reading cost to clinical investigation sponsors (one-time)	$77,766
Total reading cost of the rule (one-time)	$6,300,634
Net present value of reading costs (10 years, 3%)	**$6,117,120**
Net present value of reading costs (10 years, 7%)	**$5,888,443**
Annualized cost of reading the rule (3%)	**$717,113**
Annualized cost of reading the rule (7%)	**$838,382**

The rule will likely result in clinical investigators drafting requests for a waiver or alteration of informed consent under § 50.22 (waiver/alteration requests). As described above, we estimate that there are approximately 551 potential minimal risk clinical investigations for which a waiver/alteration request may be submitted for IRB review, that the time burden of drafting waiver/alteration requests is approximately 1 hour, and that approximately 1 investigator will draft a request for each clinical investigation. We estimate that for approximately 50 percent of the potential minimal risk clinical investigations for which a waiver/alteration request may be submitted for review, investigators will draft waiver/alteration requests, with a lower bound of approximately 25 percent and an upper bound of all potential minimal risk investigations. We multiply the number of potential minimal risk clinical investigations by the number of investigators associated with each clinical investigation and the hourly wage rate of investigators (Ref. 7) to yield an annual waiver/alteration request drafting cost of approximately $57,976 (= 551 x 1 x 1 x 0.5 x $210.44), with a lower bound of approximately $28,988 (= 551 x 1 x 1 x 0.25 x $210.44) and an upper bound of approximately $115,952 (= 551 x 1 x 1 x 1 x $210.44).

The estimated net present value of document drafting costs associated with the rule are approximately $494.5 thousand, with a lower bound of approximately $247.3 thousand and an upper bound of approximately $989.1 thousand, discounted at 3 percent over 10 years. At a 7 percent discount rate, the estimated net present value of costs is approximately $407.2 thousand, with a lower bound of approximately $203.6 thousand and an upper bound of approximately $814.4 thousand. The annualized document drafting costs associated with the rule are approximately $58.0 thousand at a 3 percent discount rate, with a lower bound of approximately $29.0 thousand and an upper bound of approximately $116.0 thousand. At a 7 percent discount rate, annualized costs are approximately $58.0 thousand, with a lower bound of approximately

$29.0 thousand and an upper bound of approximately $116.0 thousand. The estimated costs of drafting new documents in accordance with the rule are summarized in Table 4.

Table 4. Costs of Drafting New Documents (2020$)

	Low	Middle	High
Number of potential minimal risk clinical investigations	551	551	551
Percentage of potential clinical investigations affected by the rule	25%	50%	100%
Number of investigators per clinical investigation	1	1	1
Time burden of drafting waiver requests (hours)	1	1	1
Hourly wage, clinical investigators	$210.44	$210.44	$210.44
Total annual cost to investigators of drafting waiver requests	$28,988	$57,976	$115,952
Net present value of document drafting costs (10 years, 3%)	**$247,272**	**$494,549**	**$989,098**
Net present value of document drafting costs (10 years, 7%)	**$203,600**	**$407,201**	**$814,401**
Annualized cost of drafting new documents (3%)	**$28,988**	**$57,976**	**$115,952**
Annualized cost of drafting new documents (7%)	**$28,988**	**$57,976**	**$115,952**

We anticipate that affected IRBs will incur additional costs associated with the review of waiver/alteration requests and recordkeeping burdens pertaining to the rule. For purposes of estimating these costs, we retain our estimate that approximately 50 percent of potential minimal risk clinical investigations will have a waiver/alteration request and, therefore, incur related IRB review costs, with a lower bound of approximately 25 percent and an upper bound of 100 percent. We estimate the time burden of IRB review and recordkeeping for a waiver/alteration request is approximately 1 hour per investigation, including 45 minutes to review the waiver/alteration request and 15 minutes to document the IRB's determination regarding the waiver/alteration request (i.e., an IRB "recordkeeping" cost). This cost will be incurred by IRB administrators, IRB administrative staff, IRB chairs, and IRB voting members (approximately 10 per IRB as in prior calculations). We multiply the number of potential minimal risk clinical investigations by the wage rates for IRB administrators, IRB administrative staff, IRB chairs, and IRB voting members by the estimated time burden to yield a per waiver/alteration request IRB review cost of approximately $1,472.40 (= ($110.76 + $120.08 + ($120.08 x 10) + $40.76) x 1.0)

and multiply this cost by the number of investigations to yield a review and recordkeeping cost of approximately $405.6 thousand (= 551 x 0.5 x $1,472.40), with a lower bound of approximately $202.8 thousand (= 551 x 0.25 x $1,472.40) and an upper bound of approximately $811.3 thousand (= 551 x 1 x $1,472.40).

The net present value of estimated review and recordkeeping costs is approximately $3.5 million, with a lower bound of approximately $1.7 million and an upper bound of approximately $6.9 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, the net present value is approximately $2.8 million, with a lower bound of approximately $1.4 million and an upper bound of approximately $5.7 million. Annualized review and recordkeeping costs are approximately $405.6 thousand, with a lower bound of approximately $202.8 thousand and an upper bound of approximately $811.3 thousand, at 3 and 7 percent discount rates. The estimated costs of additional review and recordkeeping requirements are summarized in Table 5.

Table 5. Additional Review and Recordkeeping Costs to IRBs (2020$)

	Low	Middle	High
Number of potential minimal risk clinical investigations	551	551	551
Percent of investigations that will incur review/recordkeeping costs	25%	50%	100%
Number of investigations that will incur review/recordkeeping costs	138	276	551
Time burden of review/recordkeeping (hours)	1	1	1
Hourly wage, IRB administrator	$110.76	$110.76	$110.76
Hourly wage, IRB administrative staff	$40.76	$40.76	$40.76
Hourly wage, IRB chair	$120.08	$120.08	$120.08
Hourly wage, IRB voting member (10 members per IRB)	$1,200.80	$1,200.80	$1,200.80
Total cost of review/recordkeeping	$202,823	$405,646	$811,292
Net present value of review and recordkeeping costs (3%)	$1,730,122	$3,460,244	$6,920,489
Net present value of review and recordkeeping costs (7%)	$1,424,545	$2,849,089	$5,698,178
Total annual review and recordkeeping costs (10 years, 3%)	**$202,823**	**$405,646**	**$811,292**
Total annual review and recordkeeping costs (10 years, 7%)	**$202,823**	**$405,646**	**$811,292**

E. Cost Savings of the Rule

The rule will harmonize FDA's informed consent regulations with the Common Rule's provision for waiver or alteration of informed consent for certain minimal risk research. The proposed rule estimated that IRBs would experience a 0.5 hour reduction in the time burden of determining whether to approve a waiver of the requirement to obtain informed consent for a minimal risk clinical investigation by reviewing it under a harmonized standard; no public comments opposed or questioned this estimate. Therefore, we expect that IRBs reviewing potential minimal risk clinical investigations will experience a reduction in the time burden associated with the harmonized requirements set forth in § 50.22 and the waiver requirements in the Common Rule (45 CFR 46.116(f)).

We estimate that approximately 50 percent of potential minimal risk clinical investigations will be the subject of requests to an IRB for a waiver or alteration of informed consent as permitted by this rulemaking, with a lower bound of approximately 25 percent and an upper bound of all potential minimal risk clinical investigations. For IRB cost savings, we estimate that time savings of 0.5 hours (Ref. 9) would be incurred by one IRB administrator, one IRB administrative staff, one IRB chair, and ten IRB voting members. We multiply the number of potential minimal risk clinical investigations, the estimated reduced time burden of the rule, and the sum of each IRB wage rate to yield a total estimated cost savings to IRBs of approximately $202.8 thousand (= 551 × 0.5 × 0.5 × [$110.76 + $40.76 + ($120.08 x 10) + $120.08]), with lower bound estimated cost savings of approximately $101.4 thousand (= 551 × 0.25 × 0.5 × [$110.76 + $40.76 + ($120.08 x 10) + $120.08]) and upper bound estimated cost savings of approximately $405.6 thousand (= 551 × 1 × 0.5 × [$110.76 + $40.76 + ($120.08 x 10) + $120.08]).

The total annual cost savings of the rule to affected IRBs is approximately $202.8 thousand, with a lower bound of approximately $101.4 thousand and an upper bound of approximately $405.6 thousand. The net present value of the cost savings of the rule is approximately $1.7 million, discounted at 3 percent, with a lower bound of approximately $865.1 thousand and an upper bound of approximately $3.5 million. The net present value of the cost savings of the rule are approximately $1.4 million, discounted at 7 percent, with a lower bound of approximately $712.3 thousand and an upper bound of approximately $2.8 million. The annualized cost savings of the rule are approximately $202.8 thousand with a lower bound of approximately $101.4 thousand and an upper bound of approximately $405.6 thousand at 3 and 7 percent discount rates over 10 years. The estimated cost savings of the rule to IRBs and clinical investigators are summarized in Table 6.

Table 6. Cost Savings of the Rule to IRBs (2020$)

	Low	Middle	High
Number of potential minimal risk clinical investigations per year	551	551	551
Percentage of potential minimal risk investigations affected by the rule	25%	50%	100%
Reduced time burden of reviewing the rule (hours)	0.5	0.5	0.5
Hourly wage, IRB administrator	$110.76	$110.76	$110.76
Hourly wage, IRB administrative staff	$40.76	$40.76	$40.76
Hourly wage, IRB chair	$120.08	$120.08	$120.08
Hourly wage, IRB voting member (10 members per IRB)	$1,200.80	$1,200.80	$1,200.80
Total cost savings for the rule	$101,412	$202,823	$405,646
Net present value of the rule (3%, 10 years)	$865,061	$1,730,122	$3,460,244
Net present value of the rule (7%, 10 years)	$712,272	$1,424,545	$2,849,089
Annualized cost savings of the rule (3%)	**$101,412**	**$202,823**	**$405,646**
Annualized cost savings of the rule (7%)	**$101,412**	**$202,823**	**$405,646**

F. Non-Quantified Benefits of the Rule

The rule will amend FDA's current informed consent regulations to harmonize with the Common Rule's provision for waiver or alteration of informed consent for certain minimal risk

research. We expect benefits in the form of healthcare advances stemming from additional minimal risk clinical investigations that would proceed using a waiver or alteration of informed consent. For example, there are important clinical questions regarding the real-world effectiveness of FDA-regulated medical products that may be impracticable to address in research requiring informed consent. While we estimate the number of such investigations initiated each year will be relatively small in number, we expect their impact to be of particular value to clinical and patient communities. For example, SACHRP has recommended and reiterated in subsequent recommendations that FDA adopt the provisions for waiver or alteration of consent that exist under the Common Rule for minimal risk research, to facilitate cluster randomized trials (Ref. 10). Such trials may provide important insights about the real-world effectiveness of a one or more FDA-regulated products.

We also expect benefits from harmonization with the Common Rule's provision for waiver or alteration of informed consent for certain minimal risk research. The Common Rule provision is currently used by numerous Federal departments and agencies. Some clinical research is subject to both FDA's regulations and the Common Rule, so harmonization of this specific waiver provision will benefit those entities that conduct, sponsor, or review certain minimal risk clinical investigations by, as one public comment noted, "reducing confusion between HHS and FDA research guidelines in regards to the informed consent process," and burden created by the need to comply with differing requirements.

G. Summary of Net Cost Savings

We estimate that the annualized net cost savings of the rule are approximately -$977.9 thousand (= $202,823 - $717,113 - $57,976 - $405,646), with a lower bound of approximately -$847.5 thousand (= $101,412 - $717,113 - $28,988 - $202,823) and an upper bound of

approximately -$1.2 million (= $405,646 - $717,113 - $115,952- $811,292) at a 3 percent discount rate. At a 7 percent discount rate, the estimated annualized net cost savings of the rule are approximately -$1.1 million (= $202,823 - $838,382 - $57,976- $405,646), with a lower bound of approximately -$968.8 thousand (= $101,412 - $838,382 - $28,988 - $202,823) and an upper bound of approximately -$1.4 million (= $405,646 - $838,382 - $115,952- $811,292). The estimated costs and cost savings of the rule are summarized in Table 7.

Table 7. Summary of Costs and Cost Savings of the Rule (2020$)

	Low	Middle	High
Cost of reading the rule (annualized, 3%)	$717,113	$717,113	$717,113
Cost of reading the rule (annualized, 7%)	$838,382	$838,382	$838,382
Cost of drafting new documents (annualized, 3%)	$28,988	$57,976	$115,952
Cost of drafting new documents (annualized, 7%)	$28,988	$57,976	$115,952
Cost of review and recordkeeping (annualized, 3%)	$202,823	$405,646	$811,292
Cost of review and recordkeeping (annualized, 7%)	$202,823	$405,646	$811,292
Cost savings of the rule (annualized, 3%)	$101,412	$202,823	$405,646
Cost savings of the rule (annualized, 7%)	$101,412	$202,823	$405,646
Net cost savings of the rule (annualized, 3%)	**($847,513)**	**($977,912)**	**($1,238,712)**
Net cost savings of the rule (annualized, 7%)	**($968,781)**	**($1,099,181)**	**($1,359,980)**

II. 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. The small entities that would most likely be affected by the final rule are sponsors of drug and medical device research and medical institutions, primarily medical and surgical hospitals that are affiliated with affected IRBs. Because the final rule is unlikely to impose a substantial burden on the affected small entities, we certify that the final rule will not have a significant economic impact on a substantial number of small entities. The following analysis, as well as other sections of this document and

the preamble of the final rule, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

The small entities most likely to be affected by the final rule are medical institutions, primarily medical and surgical hospitals, affiliated with affected IRBs. To estimate the number of affiliated hospitals, we use Census Bureau data with NAICS code 622110 "General Medical and Surgical Hospitals" (Ref. 11), and the Small Business Administration definition for a small hospital of $47.0 million or less in annual revenue (Ref. 12). Based on SBA revenue threshold, we estimate that the number of small medical and surgical hospitals is 2,838 of 6,821 total hospitals, or approximately 42 percent. We estimate that 42 percent, or approximately 229 IRBs (= 0.41607 x 551) and approximately 229 sponsors of clinical investigations potentially affected by the rule (= 0.41607 x 551) are affiliated with small entities and that 42 percent of the estimated costs and cost savings of the proposed rule will be incurred by small entities.

We estimate that small entities will incur 42 percent of the net cost savings of the rule, including cost savings from reduced time burdens, reading costs, costs of drafting new waiver/alteration requests, and additional recordkeeping costs. We estimate that approximately 229 IRBs are associated with small entities and will incur annualized net cost savings of approximately -$27.1 thousand, with a lower bound of approximately -$44.2 thousand and an upper bound of approximately $6.9 thousand at a 3 percent discount rate. Discounted at 7 percent, annualized net cost savings for small entities are approximately -$37.5 thousand, with a lower bound of approximately -$54.5 thousand and an upper bound of approximately -$3.4 thousand. Annualized net cost savings per IRB associated with small entities are approximately -$118.38 (= -$27,139 / 229), with a lower bound of approximately -$192.64 (= -$44,162 / 229) and an upper bound of approximately $30.13 (= $6,908 / 229), discounted at 3 percent over 10

years. At a 7 percent discount rate, the annualized net cost savings per IRB associated with small entities are approximately -$163.61 (= -$37,486 / 229), with a lower bound of approximately -$237.77 (= -$54,509 / 229) and an upper bound of approximately -$15.00 (= -$3,439 / 229).

We estimate that approximately 229 (= 0.41607 x 551) sponsors of clinical investigations affected by the rule are small and will incur annualized net cost savings of approximately -$32.9 thousand, with a lower bound of approximately -$20.8 thousand and an upper bound of approximately -$57.0 thousand, discounted at 3 percent over 10 years. At a 7 percent discount rate, the annualized net cost savings per clinical investigations associated with small entities are approximately -$39.9 thousand, with a lower bound of approximately -$25.3 thousand and an upper bound of approximately -$69.2 thousand. Annualized net cost savings per clinical investigation associated with small entities are approximately -$143.36 (= -$32,867 / 229), with a lower bound of approximately -$90.75 (= -$20,806 / 229) and an upper bound of approximately -$248.58 (= -$56,989 / 229), discounted at 3 percent over 10 years. At a 7 percent discount rate, annualized net cost savings per clinical investigation associated with small entities are approximately -$174.12 (= -$39,917 / 229), with a lower bound of approximately -$110.22 (= -$25,269 / 229) and an upper bound of approximately -$301.91 (= -$69,214 / 229).

This analysis estimates that the per small entity effect of the final rule will take the form of negative net cost savings to small medical and surgical hospitals. Although SBA provides a maximum revenue for small medical and surgical hospitals, we lack data on the distribution of revenues for small hospitals. As a conservative estimate of the impact of the final rule on small entities, we total the lower bound estimate of negative net cost savings to yield a per small entity cost of approximately $430.40 (= $237.77 + $192.64). While we lack data on the distribution of

small medical and surgical hospital revenues, this conservative estimate of per entity net cost savings is a smaller proportion of maximum revenue than 3 percent, the threshold at which we would determine the final rule would have a significant impact on small entities. We estimate that if minimum revenues of small medical or surgical hospitals were approximately 1 percent ($470,000) of maximum revenues, our conservative net cost savings estimate of approximately $430.40 would be lower than 3 percent when expressed as a proportion of revenues. We therefore certify that the final rule will not have a significant economic impact on a substantial number of small entities. Our estimates of the effect of the rule on small entities are summarized in Table 8.

Table 8. Net Cost Savings for Small Entities (2020$)

	Low	Middle	High
Percent of affected entities that are small*	41.607%	41.607%	41.607%
Number of affected IRBs	551	551	551
Number of affected small IRBs	229	229	229
IRB cost savings (annual)	$101,412	$202,823	$405,646
IRB cost of reading the rule (one-time)	$537,584	$537,584	$537,584
IRB cost of review and recordkeeping (annual)	$84,388	$168,776	$337,553
Annualized net cost savings to small IRBs (3%, 10 years)	($44,162)	($27,139)	$6,908
Annualized net cost savings to small IRBs (7%, 10 years)	($54,509)	($37,486)	($3,439)
Annualized net cost savings per small IRB (3%)	**($192.64)**	**($118.38)**	**$30.13**
Annualized net cost savings per small IRB (7%)	**($237.77)**	**($163.51)**	**($15.00)**
Number of affected small sponsors clinical investigations	229	229	229
Investigator cost of reading the rule (one-time)	$76,833	$76,833	$76,833
Investigator cost of drafting waiver/alteration requests (annual)	$12,061	$24,122	$48,244
Annualized net cost savings to small sponsors of clinical investigations (3%, 10 years)	($20,806)	($32,867)	($56,989)
Annualized net cost savings to small sponsors of clinical investigations (7%, 10 years)	($25,269)	($39,917)	($69,214)
Annualized net cost savings per small sponsors of clinical investigation (3%)	**($90.75)**	**($143.36)**	**($248.58)**
Annualized net cost savings per small clinical investigation (7%)	**($110.22)**	**($174.12)**	**($301.91)**

*NAICS 622110, "General Medical and Surgical Hospitals"

III. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. 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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2. U.S. Department of Health and Human Services, "Guidelines for Regulatory Impact Analysis", 2016, available at: https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis, accessed May 12, 2023.

3. U.S Government Publishing Office, "Federal Policy for the Protection of Human Subjects", 82 FR 7149 (January 19, 2017), available at: https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf, accessed May 12, 2023.

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10. SACHRP, Recommendation to the Secretary of HHS, "Recommendations on Regulatory Issues in Cluster Randomized Studies" (October 26, 2016). Available at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html. Accessed on October 5, 2023.

11. 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 May 12, 2023.

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https://www.sba.gov/sites/default/files/2022-05/Table%20of%20Size%20Standards_Effective%20May%202%202022_Final.pdf accessed May 12, 2023.