that the action is incorporated by reference under 1 CFR part 51. As a result, the final rule correction is being withdrawn.

Lists of Subjects in 14 CFR Part 73

Airspace, Prohibited areas, Restricted areas.

The Withdrawal

■ The FAA determined that the final rule correction published in the **Federal Register** on December 6, 2023 (88 FR 84695) contains incorrect references. Therefore, the FAA withdraws that final rule correction.

Issued in Washington, DC, on December 15, 2023.

Brian Konie,

Acting Manager, Rules and Regulations Group.

[FR Doc. 2023–28032 Filed 12–20–23; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 312, and 812

[Docket No. FDA–2018–N–2727]

RIN 0910–AH52

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to amend its regulations to implement a provision of the 21st Century Cures Act (Cures Act). This final rule allows an exception from the requirement to obtain informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. The final rule permits an institutional review board (IRB) to waive or alter certain informed consent elements or to waive the requirement to obtain informed consent, under limited conditions, for certain FDA-regulated minimal risk clinical investigations.

DATES: This rule is effective January 22, 2024.

ADDRESSES: For access to the docket to read background documents or comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the heading of this final rule into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Lauren Milner, Office of Clinical Policy, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 301–796–5514, *lauren.milner@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Final Rule

This final rule implements the statutory changes made to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the Cures Act to allow for a waiver or alteration of informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. The rule will permit an IRB to waive or alter certain informed consent elements or to waive the requirement to obtain informed consent, under limited conditions, for certain minimal risk clinical investigations.

B. Summary of the Major Provisions of the Final Rule

The final rule amends FDA's regulations to allow IRBs 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. For an IRB to approve a waiver or alteration of informed consent requirements for minimal risk clinical investigations, the rule requires an IRB to find and document five criteria that are consistent with the revised rule entitled ''Federal Policy for the Protection of Human Subjects'' (the revised Common Rule (January 19, 2017)). FDA believes the amendment provides appropriate safeguards to protect the rights, safety, and welfare of the human subjects participating in such clinical investigations. We are also making conforming amendments to FDA's regulations.

C. Legal Authority

Sections 505(i)(4) and 520(g)(3) of the FD&C Act, as amended by the Cures Act, in conjunction with FDA's general rulemaking authority in section 701(a) of the FD&C Act, serve as FDA's principal legal authority for this rule. In addition, the Cures Act directs the Secretary of the Department of Health and Human Services (HHS) to ''harmonize differences between the HHS Human Subject Regulations and the FDA Human Subject Regulations,'' to the extent practicable and consistent with other statutory provisions.

D. Costs and Benefits

This rule will help enable the conduct of certain minimal risk clinical investigations for which the requirement to obtain informed consent is waived or for which certain elements of informed consent are waived or altered.

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 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 to IRBs 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 that would not be performed without a waiver or alteration of informed consent. We cannot quantify all benefits that might arise from such studies because of the lack of relevant data available regarding the focus of these types of studies that will support regulatory submissions to FDA.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation	What it means
Cures Act	21st Century Cures Act (Pub. L. 114–255).
FDA or the Agency	U.S. Food and Drug Administration.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
HHS	U.S. Department of Health and Human Services.
HIPAA Privacy Rule	Health Insurance Portability and Accountability Act Privacy Rule (45 CFR Part 160 and 45 CFR Part 164, Subparts A and E).
IDE	Investigational Device Exemption.
IRB	Institutional Review Board.
IVD	In Vitro Diagnostic.
LAR	Legally Authorized Representative.
OHRP	Office for Human Research Protections.
OMB	U.S. Office of Management and Budget.
PHI	Protected Health Information.
PRA	Paperwork Reduction Act of 1995.
RWD	Real-world data.
SACHRP	Secretary's Advisory Committee on Human Research Protections.

III. Background

A. Need for the Regulation/History of This Rulemaking

In the **Federal Register** of November 15, 2018 (83 FR 57378), FDA issued a proposed rule to revise our informed consent regulations at part 50 (21 CFR part 50) to permit an IRB to waive or alter certain informed consent elements or to waive the requirement to obtain informed consent, under limited conditions, for certain FDA-regulated minimal risk clinical investigations. As described in the proposed rule, FDA's current regulations governing the protection of human subjects (parts 50 and 56 (21 CFR parts 50 and 56)) require that a human subject, or the subject's legally authorized representative (LAR), provide informed consent before the subject participates in a clinical investigation, and only allow exception from the general requirements of informed consent in certain life-threatening situations or by Presidential waiver for certain military operations when specific conditions are met (§ 50.23 (21 CFR 50.23)) or when the requirements for emergency research are met (§ 50.24 (21 CFR 50.24)).

On December 13, 2016, the Cures Act (Pub. L. 114–255) was signed into law. Section 3024 of the Cures Act amended sections 505(i)(4) and 520(g)(3) of the FD&C Act (21 U.S.C. 355(i)(4) and 360j(g)(3)) to provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. This rule implements the statutory change by allowing an additional exception from the general requirements of informed consent for certain FDA-regulated clinical investigations.

In addition, section 3023 of the Cures Act directs the Secretary of the Department of Health and Human Services (HHS) to ''harmonize differences between the HHS Human Subject Regulations and the FDA Human Subject Regulations,'' to the extent practicable and consistent with other statutory provisions. This rule harmonizes [1] FDA's requirements for waiver or alteration of informed consent for minimal risk clinical investigations with the revised Common Rule's requirements under 45 CFR 46.116(f)(3). The Common Rule has included four criteria for waiver or alteration of informed consent for minimal risk research since it was originally issued in

[1] The term ''harmonize,'' as used in this proposed rule means, ''harmonize to the extent practicable and consistent with other statutory provisions,'' consistent with section 3023 of the Cures Act.

1991 (56 FR 28001, June 18, 1991). When the Common Rule was revised (82 FR 7149, January 19, 2017),[2] a fifth criterion was added, *i.e.,* ''[i]f the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format'' (45 CFR 46.116(f)(3)(iii)). FDA proposed to adopt the four criteria from the 1991 version of the Common Rule and solicited comment on whether to adopt the fifth criterion (83 FR 57378, November 15, 2018).

On July 25, 2017, FDA issued a guidance document entitled ''IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects'' (IRB Waiver or Alteration of Informed Consent Guidance) (82 FR 34535). This guidance informs sponsors, investigators, and IRBs that FDA does not intend to object to an IRB waiving or altering informed consent requirements, as described in the guidance, for certain minimal risk clinical investigations. In addition, the guidance informs sponsors, investigators, and IRBs that FDA 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. FDA intends to withdraw the guidance after the regulations in this rule become effective.

FDA is issuing this final rule to permit an IRB waiver or alteration of informed consent in limited circumstances, consistent with the Cures Act. We believe that this rule will both safeguard the rights, safety, and welfare of human subjects and enable minimal risk clinical investigations that may facilitate medical advances and promote public health. In addition, because some clinical research is subject to FDA and other federal requirements under the Common Rule, harmonization of this waiver provision should also provide clarity for and reduce burden on the research community.

[2] For the purposes of this final rule, 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 and general compliance date (83 FR 2885, January 22, 2018) and the final rule that further 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).

B. Summary of Comments to the Proposed Rule

We received fewer than 50 comment letters to the proposed rule from academia, IRBs, public advocacy groups, industry, trade organizations, public health organizations, individuals, and other organizations. FDA received comments on topics that included the following: (1) general support or opposition to the rule; (2) definitions and descriptions of the criteria listed in the rule; (3) adopting the fifth criterion from the revised Common Rule; (4) secondary research involving biospecimens; (5) examples of clinical investigations that might meet the proposed waiver criteria; (6) requests for specific and/or additional guidance on the rule; (7) the expedited review list and IRB continuing review; (8) cost savings of the proposed rule; and (9) the proposed effective date of the rule.

C. General Overview of the Final Rule

In this rulemaking, FDA is finalizing its proposal to add new § 50.22, ''Exception from informed consent requirements for minimal risk clinical investigations'' to part 50 and make three conforming amendments to §§ 50.20, 312.60, and 812.2 (21 CFR 50.20, 312.60, and 812.2) of our current regulations to reflect the exception from informed consent for certain minimal risk clinical investigations. In addition, based on comments received on the proposed rule, FDA is adding the criterion at § 50.22(c), which addresses clinical investigations involving identifiable private information or identifiable biospecimens. As described below, FDA changed the order of the criteria in § 50.22 to match the order of the revised Common Rule's requirements for general waiver or alteration of consent (45 CFR 46.116(f)(3)). FDA also made minor organizational and editorial changes to § 50.22 to increase clarity and consistency with the regulatory text of the revised Common Rule.

- FDA made a minor editorial change to the introductory text to § 50.22 for clarity. Specifically, we revised the text ''or that waives'' to read ''or may waive.'' The regulation permits the IRB responsible for the review, approval, and continuing review of the clinical investigation to approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent in § 50.25(a) and (b) of FDA's current regulations, or to waive the requirement to obtain informed consent, provided that the IRB finds and documents five criteria under § 50.22(a) through (e).
- In § 50.22(a), FDA finalizes the criterion as proposed that the clinical investigation involves no more than minimal risk to the subjects.
- In § 50.22(b), FDA adopts the criterion that was proposed at § 50.22(c) and adds the word ''requested'' for clarity and to harmonize with the text of the revised Common Rule at 45 CFR 46.116(f)(3)(ii) (*i.e.,* the clinical investigation could not practicably be carried out without the requested waiver or alteration).
- Based on comments received on the proposed rule (see section V.D. of this final rule), FDA is finalizing this rule with the additional criterion at § 50.22(c) that states that if the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format.
- In § 50.22(d), FDA adopts the criterion that was proposed at § 50.22(b) that states that the waiver or alteration will not adversely affect the rights and welfare of the subjects.
- In § 50.22(e), FDA adopts the criterion that was proposed at § 50.22(d) and adds ''or legally authorized representatives'' to the criterion (*i.e.,* whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation) to align with the revised Common Rule and to make clear to whom additional information may be provided.
- Three conforming amendments to §§ 50.20, 312.60, and 812.2 of our current regulations are finalized as proposed. FDA received no public comments on these three proposed conforming amendments. The introductory clause of § 50.20, General requirements for informed consent, is revised to include reference to § 50.22 as one of the limited exceptions to the general requirements for informed consent. The second sentence in § 312.60, General responsibilities of investigators, is revised to reference part 50 generally rather than list each specific exception to the informed consent requirements in part 50. This simplifies the regulatory text and makes it clear that the investigator is responsible for obtaining the informed consent of each human subject to whom the drug is administered in accordance with part 50, which includes § 50.22. Similarly, in part 812, Investigational Device Exemptions (IDEs), § 812.2(b)(1)(iii) is revised to make clear that the investigator must obtain informed consent in accordance with part 50, which includes § 50.22. In

addition, to simplify the current regulatory text, we removed the reference to documentation being waived under § 56.109(c) (21 CFR 56.109(c)), as the relevant section of the regulations in part 50 (*i.e.,* § 50.27 (21 CFR 50.27)) refers to § 56.109(c) and need not be repeated.

IV. Legal Authority

Title III, section 3024 of the Cures Act amended sections 505(i)(4) and 520(g)(3) of the FD&C Act to provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. This statutory amendment was signed into law and became effective on December 13, 2016. These regulations reflect these statutory changes to the FD&C Act, including appropriate human subject protection safeguards. Thus, sections 505(i)(4) and 520(g)(3) of the FD&C Act, as amended by section 3024 of the Cures Act, in conjunction with FDA's general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as our principal legal authority for this rule. In addition, Title III, section 3023 of the Cures Act provides that the Secretary of Health and Human Services shall ''harmonize differences between HHS Human Subject Regulations and FDA Human Subject Regulations'' to the extent practicable and consistent with other statutory provisions.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received fewer than 50 comment letters on the proposed rule by the close of the comment period. We received comments from academia, IRBs, public advocacy groups, industry, trade organizations, public health organizations, individuals, and other organizations.

We describe and respond to the comments below. Comment summaries are numbered, with similar comments grouped together under the same number. In some cases, different issues discussed in the same comment letter were designated as distinct comments for purposes of our responses. The number assigned to each comment summary or comment topic is purely for organizational purposes and does not signify the comment's value or importance, or the order in which comments were received.

B. Description of General Comments and FDA Response

FDA proposed to amend its regulations to allow the IRB responsible for the review, approval, and continuing review of FDA-regulated clinical investigations to approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent set forth in § 50.25(a) and (b), or that waives the requirement to obtain informed consent, provided that the IRB finds and documents that four criteria are met. FDA also solicited public comment on the inclusion of a fifth criterion and asked for comment on the types of FDA-regulated minimal risk clinical investigations for which sponsors would anticipate requesting a waiver or alteration of informed consent from the IRB.

(Comment 1) A majority of general comments favor the Agency's efforts to harmonize FDA's human subject protection regulations with the revised Common Rule. These comments generally support the proposed rule because it would reduce administrative burdens on IRBs and researchers, reduce research costs, facilitate valuable research, or address public health concerns without compromising subjects' rights, safety, or welfare.

Several comments express support for harmonization with the revised Common Rule's provision for waiver or alteration of informed consent to reduce burdens related to conducting certain types of research, including some cluster randomized or pragmatic trials, and enabling learning health systems, in which clinicians continually learn from data collected at the point of care. One comment indicates that such research has the potential to contribute in important ways to the evidence base regarding drug and device efficacy, while another suggests that finalizing the proposal would result in more and better data regarding the risks and benefits of drugs and devices in real-world settings. An additional comment argues that a waiver of informed consent may be necessary and ethically justifiable for certain types of clinical investigations that are critical for medical advancement, patient care, and safety.

Other comments support the proposal because certain minimal risk investigations are difficult or impossible to carry out if consent is required, such as certain secondary research involving biospecimens that may lead to important medical advances toward personalized medicine; research involving retrospective records reviews; and research involving no more than minimal risk to subjects that would not qualify for an exception from informed consent under § 50.24 of FDA's current regulations because participation would not hold out a prospect of direct benefit to the subjects. The comments point out that current FDA regulations permit waivers from the requirement to obtain informed consent only under limited circumstances.

(Response 1) FDA agrees that this rule will facilitate investigators' ability to conduct certain minimal risk clinical investigations that could lead to healthcare advances through development of products to diagnose or treat diseases or other conditions, without compromising subjects' rights, safety, or welfare. To the extent that the studies described in the comments would constitute FDA-regulated clinical investigations that could not be carried out under our current regulations, we agree that this final rule may help enable such research and that a waiver of informed consent is ethically justifiable for certain types of investigations.

In addition, FDA expects that this final rule will reduce administrative burdens on IRBs and researchers and reduce research costs. For example, harmonization with the revised Common Rule's general provision for waiver or alteration of informed consent will allow IRBs that review minimal risk clinical research subject to both FDA's regulations and the revised Common Rule to use the same criteria for reviewing a request for a waiver or alteration of informed consent for a clinical investigation. This should minimize the need for separate processes for review of such requests.

(Comment 2) Of the comments that oppose the proposed rule, two oppose it because they assert that waiving consent conflicts with existing ethical and international standards, such as the Belmont Report, the Nuremberg Code, the Declaration of Helsinki, and the International Covenant on Civil and Political Rights (ICCPR). Two other comments suggest that FDA withdraw the proposal because the underlying law and revised Common Rule are defective and ''against the spirit'' of human subject protection.

(Response 2) FDA disagrees with the comments opposing the rule. We believe that the rule upholds the principles underlying existing ethical standards, while accounting for advances in the conduct of FDA-regulated clinical investigations. It is also consistent with the obligations of the ICCPR and the U.S.' reservations, declarations, and understandings to the Covenant (see,

e.g., Ref. 1). The standards referenced in the comments emphasize the importance of voluntary informed consent for research participants. As stated in the proposed rule, obtaining informed consent from those who volunteer to participate in research is a fundamentally important principle of human subject protection. However, there are some situations in which important research cannot practicably be conducted if informed consent is required. This rule permits a waiver of consent in limited circumstances, consistent with the statutory amendments Congress made in section 3024 of the Cures Act. The waiver is only permitted in circumstances where the risks posed to subjects by the research are minimal and where an IRB has reviewed the research and determined, among other things, that the waiver or alteration will not adversely affect the rights and welfare of subjects. If research can be practicably carried out without a waiver of informed consent, investigators cannot obtain a waiver under this rule.

Additionally, the ethical principles identified in many of the national and international guidelines for research conduct, such as the three ethical principles described in the Belmont Report (respect for persons, beneficence, and justice), should be considered and weighed within the context of a particular clinical investigation, as the consideration of each principle depends on multiple factors associated with the investigation, such as research methodologies or participant populations. This rule permits a waiver or alteration of consent only in limited circumstances where the risks posed to subjects by the research are very low. We believe that with the protections in place under this rule (including the requirement for an IRB to find and document that the waiver or alteration will not adversely affect the rights and welfare of subjects), the balance between respect for persons and beneficence should come out in favor of facilitating research that satisfies the criteria in § 50.22 by permitting waiver or alteration of informed consent requirements to advance the public health. Additionally, although informed consent is a critical element of FDA's regulations that reflects the principle of respect for persons through the exercise of autonomy, we believe that the criteria provided in this rule also reflect the principle of respect for persons. For example, in a minimal risk clinical investigation for which an IRB waives consent, ensuring that the rights and welfare of subjects are not adversely affected by the waiver demonstrates respect for persons, as does providing additional pertinent information about the investigation to subjects whenever appropriate (Ref. 2).

Finally, FDA declines to withdraw the proposed rule in response to the comments that disagree with section 3024 of the Cures Act and the revised Common Rule. The Common Rule's provisions for waiver or alteration of informed consent for minimal risk research have been in effect for over 30 years and have provided appropriate safeguards to protect the rights and welfare of human subjects. As noted above, FDA believes that this rule provides an important mechanism for conducting clinical investigations that will both appropriately safeguard human subjects and potentially lead to medical advances that serve the public health.

(Comment 3) Some comments suggest that conducting research without informed consent would violate the U.S. Constitution or weaken constitutionally guaranteed rights. One comment argues that ''invasive procedures, interventions or intrusions'' into a person's ''body, cognition, or otherwise'' without consent is a violation or a potential violation of the Fourth, Fifth, Eighth, and Fourteenth Amendments. A second comment asserts that waiving consent for research involving physical interventions would violate the Fourth and Fifth Amendments and requested clarification that Constitutional rights are among the rights at issue when considering whether the proposed criteria for waiver of consent are satisfied. Another comment indicates that a waiver of informed consent would constitute an unwanted bodily invasion and that individuals have a constitutional right to privacy that protects them against such invasions. Other comments make general statements questioning the constitutionality of a waiver of informed consent.

(Response 3) We disagree with comments suggesting that the rule is unconstitutional. With respect to the comments that make only a general assertion that the rule may violate the Constitution or weaken constitutional rights, the lack of additional detail regarding the grounds for this assertion makes it impossible to provide a further substantive response. One comment cites a Federal district court case, *Merriken* v. *Cressman,* 364 F. Supp. 913 (E.D. Pa. 1973), for the general proposition that Federal courts have applied a requirement for fully voluntary informed consent grounded in constitutional law to social, behavioral, and biomedical research. Contrary to the comment's assertion, however, the court did not decide in *Merriken* whether informed consent is required for participation in all research as a general matter. The case involved a program designed to help a school district identify potential drug abusers. *Id.* at 914. The court found that part of this program represented an invasion of an individual constitutional right to privacy that was not outweighed by the government's public need for the information. *Id.* at 918, 921. The court then went on to address the standard for and adequacy of consent to waive a constitutional right to privacy involving an invasion of the parent-child relationship, rather than consent to participate in FDA-regulated minimal risk research. *Merriken* does not prevent FDA from finalizing this rule.

Of those comments that identify particular constitutional Amendments or rights, none provides specific facts or a legal basis for their claims that the rule would violate those provisions or rights. We are thus unable to provide a specific response to those comments. However, we note that the rule does not require an IRB to waive or alter informed consent, nor does it require any entity, including a government entity, to conduct or support any research. Therefore, to the extent that conducting a particular clinical investigation with a waiver or alteration of informed consent could be viewed as interfering with a constitutional right, this rule does not require an IRB to grant such a waiver or alteration or require that the research be conducted. In addition, we are clarifying, as requested by one comment, that constitutional rights are among the rights that may be appropriate for an IRB to consider when determining if the criterion in § 50.22(d) of the final rule (which requires the IRB to find that ''[t]he waiver or alteration will not adversely affect the rights and welfare of the subjects'') is satisfied.

Finally, we note that some of the comments that question the constitutionality of the rule appear to be concerned about potential waivers of informed consent for research involving ''invasive procedures.'' It is important to emphasize that the provision for a waiver or alteration of informed consent being finalized in this rule is available only for clinical investigations that involve no more than minimal risk to the subjects and meet the other criteria in § 50.22. In general, we do not believe that a study involving an invasive procedure being used for research

purposes would qualify as presenting no more than minimal risk to subjects.[3]

(Comment 4) A few comments oppose the proposal because it would not restrict or prohibit waiver of consent for classified research, citing President Clinton's Memorandum of 1997 regarding classified research (''Clinton Memorandum,'' Ref. 3).

(Response 4) We do not believe it is necessary to address classified research in this rulemaking. As noted in some of these comments, the Clinton Memorandum is directed to Agencies that may conduct or support classified research subject to the 1991 Common Rule. FDA's informed consent regulations apply to all clinical investigations, as defined in § 50.3(c) (21 CFR 50.3(c)), involving FDA-regulated articles. FDA does not regulate research on the basis that it is federally conducted or supported. To the extent a Federal Agency conducts or supports classified research and prohibits waiver of informed consent for such research, FDA's new waiver provision at § 50.22 does not require any IRB to waive informed consent and thus would not conflict with the prohibition.

(Comment 5) Several comments argue that waivers of informed consent weaken human subject protections and would allow IRBs to retreat from their human subject protection responsibilities. These comments also express concern that the proposal might decrease public trust in both research and healthcare providers. One comment states that no third parties, including IRBs, should be allowed to make decisions for study subjects as to what constitutes ''minimal risk.''

(Response 5) We do not agree that providing a waiver or alteration of informed consent under the limited circumstances described in the rule would allow IRBs to retreat from their human subject protection responsibilities or that such waivers or alterations will decrease public trust in research and healthcare providers. IRBs have been making similar waiver and alteration decisions for research subject to the Common Rule since its issuance in 1991, and the comments do not provide evidence that such decisions have decreased overall public trust in either research or healthcare providers. As noted above, this rule provides appropriate safeguards to protect the rights, safety, and welfare of human subjects when consent is waived and thus waivers granted in accordance with § 50.22 should not weaken public trust.

We also disagree with the comment stating that IRBs should not be allowed to make decisions as to what research constitutes ''minimal risk.'' IRBs have considerable experience making ''minimal risk'' determinations under FDA regulations (see response to Comment 10). For example, IRBs have been making minimal risk determinations for decades to decide whether expedited review procedures may be used for certain categories of research (see § 56.110(b)(1) (21 CFR 56.110(b)(1)); 63 FR 60353, November 9, 1998) and when reviewing clinical investigations involving children as subjects (see part 50, subpart D). In light of this experience, we believe that IRBs are generally well-positioned to determine what constitutes ''minimal risk'' to subjects when considering the details of a particular clinical investigation.

(Comment 6) Several comments criticize the proposal as too vague and subjective. These comments recommend adding definitions or providing further description of the criteria in § 50.22. They also recommend clarifying or providing examples of research for which a waiver or alteration would be allowed under the proposal in order to reduce the potential for inconsistency and variability in IRBs' decision making.

(Response 6) We do not agree with the comments stating that this rule is too vague and subjective. The five criteria in § 50.22 for a waiver or alteration of informed consent for minimal risk clinical investigations are harmonized with the revised Common Rule's criteria in 45 CFR 46.116(f)(3). We note that four of these criteria have been included in the Common Rule and have been successfully applied since the Common Rule was originally issued in 1991. The revised Common Rule added a fifth criterion (45 CFR 46.116(f)(3)(iii)), which corresponds to § 50.22(c) in this rule. That fifth criterion was modeled on a comparable criterion in the HIPAA Privacy Rule, which requires, as a condition of waiver of the requirement to obtain an individual's authorization, that the research could not practicably be conducted without access to and use of protected health information (PHI) (see 82 FR 7149 at 7224).[4] We believe that alignment between the HIPAA Privacy Rule, the revised Common Rule, and part 50 will support consistent application of the criterion in § 50.22(c) by the research community.

In response to the comments recommending additional definitions or criteria descriptions, we note that throughout this document (for example, see FDA responses to comments 10, 12, 13, and 16) we address comments requesting the addition of specific definitions or further clarification for each of the criteria described in § 50.22. FDA intends to issue further guidance to assist IRBs in applying these criteria to clinical investigations with additional information on the types of clinical investigations that may qualify for a waiver or alteration of consent under § 50.22.

(Comment 7) Some comments address implementation-related aspects of the proposed waiver or alteration provision. One comment, noting that subjects may already be giving consent to undergo non-research related patient care, questions why it would not also be appropriate to obtain their consent for research-related interventions at the same time. Another comment questions how a person reviewing hospital records would know a subject agreed to be in the study if consent had been waived.

(Response 7) With respect to the comment that questions why consent would need to be waived if informed consent to participate in research could be obtained at the same time that non-research related consent for patient care was being obtained, FDA notes that that the investigation would need to be impracticable to perform without a waiver in order to qualify for a waiver under this final rule. As stated in the preamble to the proposed rule, if scientifically sound research can practicably be carried out using only consenting subjects, we believe it should be carried out without involving nonconsenting subjects (83 FR 57378 at 57382). Waivers or alterations of informed consent under § 50.22 are intended for situations where it is impracticable to carry out the clinical investigation, as designed, without the waiver or alteration. There may be certain cases in which getting consent from a subset of individuals in the target study population may be possible, but the study may still be considered impracticable without a waiver because of obstacles[5] to obtaining consent from a sufficient number of the subjects needed to carry out the study as designed.

[3] Certain procedures, such as blood sampling that involves simple venipuncture, are considered noninvasive for purposes of FDA's IDE regulations (§ 812.3(k) (21 CFR 812.3(k)), and research involving such procedures may be considered no more than minimal risk for the purpose of expedited review (63 FR 60353 at 60355, November 9, 1998) (see response to Comment 20).

[4] See also 45 CFR 164.512 (Uses and disclosures for which an authorization or opportunity to agree or object is not required).

[5] Please refer to FDA's response to comment 13 for more information on FDA's interpretation of the term ''practicably.''

With respect to the comment that questions how a person reviewing hospital records would know a subject agreed to be in the study if consent had been waived, any person reviewing the data for purposes of the study would be themselves an investigator or otherwise involved in the investigation, and should therefore be aware that an IRB had approved the study, found the criteria under § 50.22 were met, and granted a waiver of the requirement to obtain informed consent. This would provide that person with assurance that the subject's rights, safety, and welfare are protected. Additionally, in the event of concerns about including a particular subject or group of subjects in a clinical investigation for which informed consent has been waived in accordance with § 50.22, the investigator or member of the study team could consult appropriate parties, such as the sponsor or the IRB, to address those concerns.

(Comment 8) Two comments suggest additional requirements for studies in which consent is waived. One comment cites a research paper that assesses the legitimacy of waivers of consent for research, which the authors posit is ''predicated on the reasonable belief that potential subjects would agree if they were asked and capable of consent.'' The paper includes a literature review and qualitative assessment of studies examining participation and refusal rates in human subjects research (Ref. 4). From this review, the authors conclude that there is reason to believe that many potential participants would not want to be enrolled in a study for which informed consent is waived, if asked. The paper concludes that waivers of informed consent should be rare, and that IRBs and researchers must find out if a study is acceptable to the target population and in the community where the proposed research takes place. The comment states that ''waivers of informed consent may be granted for a population based on general characteristics of the population that make getting consent from everyone impracticable, with express acknowledgement that securing consent from some members of the population may be quite feasible and practicable, and in those cases consent must be secured.'' The comment notes that this approach is modeled on the exception from informed consent in FDA's emergency research regulations at § 50.24, and states that § 50.24 is legally and ethically superior to the waiver provision in the proposed rule. Finally, the comment recommends that an additional requirement be added to the proposed regulations requiring that consent should be secured from individuals or their LARs ''when practicable.''

A second comment suggests that, for any research for which the requirement to obtain informed consent would be waived under the provision in the proposed rule, FDA require the drafting of an ''as if'' consent form in language geared toward the subject's viewpoint before the research begins. This comment argues a precedent for this approach under § 50.24(a)(6). It also asserts that this exercise would prevent practitioners from being deprived of a description of research interventions and would describe the intervention in language geared toward the viewpoint of the human subject, which may enhance human subject protections and promote an atmosphere of appropriate respect and empathy for non-consenting human subjects.

(Response 8) With regard to the points outlined in the cited research paper, we agree that the acceptability of the research to potential participants is an important consideration for an IRB when determining whether to grant a waiver or alteration of informed consent under the final rule. FDA stated in the preamble of the proposed rule that, to make the finding that the waiver or alteration will not adversely affect the rights and welfare of the subjects, IRBs may consider, for example, whether the subject population in general would be likely to object to a waiver or alteration being granted for the research in question (83 FR 57378 at 57381 to 57382). However, individual decisions to participate in research often depend on different factors, such as the recruitment method used (Ref. 5) and health literacy (Ref. 6). Additionally, an individual's trust (or distrust) in their healthcare provider and/or in the institution conducting the research may also contribute to their willingness to participate (Ref. 7). Requiring IRBs to determine and researchers to establish that an ''appropriate majority'' of the target study population would choose to participate before granting a waiver of consent, as the article suggests, would involve accounting for the individualized factors underlying such decisions. This would be unduly burdensome and could create significant limitations or delays for minimal risk investigations that § 50.22 is intended to facilitate. Given the complexities and unknowns surrounding individual reasons for participation or refusal to participate in minimal risk research, we believe that this rule strikes an appropriate balance between enabling important research to proceed while safeguarding the rights, safety, and welfare of subjects such that consent (or elements of consent) can be appropriately waived.

FDA declines to adopt the commenter's suggestion to include in the final rule a requirement to obtain consent from individual potential subjects or their LARs ''when practicable.'' FDA's provision for exceptions from informed consent for emergency research requires, among other things, an investigator commitment to attempt to contact an LAR for each subject within the therapeutic window and, if feasible, to ask the LAR for consent within that window (§ 52.24(a)(5)). However, we disagree with the commenter's conclusion that because of this requirement, § 50.24 is ''superior'' to the requirements for a waiver under § 50.22. Each of these provisions was developed to address significantly different types of clinical investigations. The criteria listed in § 50.24 are intended for research involving a study population with no capacity to consent, in a setting where the emergency circumstances require prompt action and generally provide insufficient time and opportunity to locate and obtain consent from each subject's legally authorized representative. Specifically, for research to qualify to be conducted under § 50.24 certain conditions, including the following, must be satisfied: the subject is in a life-threatening situation; available treatments are unproven or unsatisfactory; participation in the research holds out the prospect of direct benefit to the subject; obtaining informed consent from the subject is not feasible because the subject cannot provide consent due to their medical condition; and the intervention must be administered before consent can be obtained from the subject's LAR. In contrast, the criteria for waiver or alteration of consent in § 50.22 are intended for research in which the risk to participants is minimal and are not focused on research where subjects are in a life-threatening situation. We, therefore, conclude that revising § 50.22 in this final rule to include a requirement similar to that found in § 50.24(a)(5) is not appropriate for the minimal risk research that would otherwise qualify for a waiver or alteration of informed consent under this final rule. In addition, the comment's suggestion that FDA require informed consent to be obtained from individual subjects or their LARs ''when practicable'' could cause confusion, given that the criterion at § 50.22(b) requires an IRB to find that the research could not practicably be carried out

without the requested waiver or alteration of consent. Including such a requirement would also be an unnecessary difference from the corresponding provision under the Common Rule at 45 CFR 46.116(f)(3), contrary to the harmonization goals of this rulemaking. Because §§ 50.24 and 50.22 are intended for different types of research with different ethical considerations, we believe that differences between these provisions are appropriate and that both provisions protect the rights, safety, and welfare of study subjects through the requirements that must be met for approval by an IRB.

We also decline the suggestion to require the drafting of an ''as if'' informed consent form (*i.e.,* a form that would not actually be used to obtain consent) if an IRB waives the informed consent requirement for a clinical investigation that meets the § 50.22 criteria. Although the commenter points to § 50.24(a)(6) as precedent, that provision requires IRB approval of informed consent procedures and an informed consent document that are to be used to obtain consent from a subject or LAR, when feasible. This requirement recognizes that some emergency research conducted under § 50.24 ''may include a limited number of subjects for whom a representative is able to provide surrogate consent for the subject, and the treatment window may be such to permit such consent to be obtained.'' (60 FR 49086 at 49095, September 21, 1995.) As explained above, FDA is not including a requirement in § 50.22 that the investigator obtain consent from subjects or LARs if feasible similar to the requirement in § 50.24(a)(5). Development of an ''as-if'' informed consent form that would not be used would impose additional burdens on IRBs and investigators without a clear benefit. For investigations in which informed consent is waived, we have no evidence that an ''as if'' consent document would provide practitioners with additional information or understanding of the research beyond what is available in the research protocol, or that this additional document would foster additional empathy or respect for subjects whose consent is waived. Additionally, we disagree that an ''as if'' informed consent form would increase human subject protections beyond the requirements listed in § 50.22, such as the requirement that the waiver or alteration not adversely affect the rights and welfare of subjects, as well as the requirement that, whenever appropriate, the subjects or their LARs are provided with additional pertinent information after participation.

(Comment 9) Two comments suggest tracking the cumulative effects of minimal risk studies on subjects who have participated in more than one such study and suggest establishing a centralized registry containing the names of all human subjects who are involved in research or clinical investigations, the names of the sponsor and researcher, whether the research is classified, and whether informed consent was waived or altered.

(Response 9) We decline to adopt the suggested requirement that all participants in minimal risk studies be tracked and the suggestion to establish a centralized registry of participants in clinical investigations because, among other issues (*e.g.,* the time and resources needed to establish and maintain a registry with appropriate procedures for the collection, use, and disclosure of identifiable information), such a registry might present additional risks regarding privacy and confidentiality of participant data (*e.g.,* data leak of private health information, creating links between individual data that otherwise would not exist, increased chance of stigmatization through identification of individual data collected in the registry).

C. Comments on the Proposed Waiver or Alteration Criteria

FDA proposed that, to permit a waiver or alteration of the informed consent requirements, the IRB must find and document that the following four criteria are met: (1) the clinical investigation involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the clinical investigation could not practicably be carried out without the waiver or alteration; and, (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

1. The Clinical Investigation Involves No More Than Minimal Risk to the Subjects (Proposed § 50.22(a))

The proposed rule included, as the first criterion, that the clinical investigation involves no more than minimal risk to the subjects. ''Minimal risk'' is defined in § 50.3(k) to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(Comment 10) Fewer than half of the comments reference proposed § 50.22(a) or mention the minimal risk criterion. The majority of these comments support an IRB's ability to approve informed consent procedures that do not include or that alter some of the elements of informed consent, or to waive consent entirely, for minimal risk research. Some of these comments support the ability to waive or alter informed consent requirements for specific types of research they identify as minimal risk, including research involving clinical record reviews or secondary use of biospecimens, and certain cluster randomized trials. One comment expresses trust in IRBs' abilities to know when informed consent is required.

Conversely, some comments oppose or express reservations about allowing waiver or alteration of consent for minimal risk studies, suggesting that the term ''minimal risk'' is vague, ambiguous, or subjective, or express other confusion about its meaning. One comment indicates concern that the vagueness of the term ''minimal risk'' would precipitate misuse of the rule. Other comments suggest that the rule clarify the meaning of specific terms in the definition of minimal risk (*e.g.,* ''routine physical or psychological examinations or tests''). These comments also suggest that FDA clarify that the ''daily life'' risk standard in the current definition so that IRBs would know how to interpret the standard to avoid allowing populations that encounter higher risks in daily life (*e.g.,* live in a dangerous region) to be exploited. Another comment raises concerns regarding the subjective nature of the definition of ''minimal harm'' and the potential for variability in IRB decisions on requests for waivers of informed consent.

Several comments assert that IRBs should not be entrusted to make minimal risk determinations. A few comments suggest that determinations of risk are subjective and that only the individual subject can make a meaningful decision about degrees of risk and whether a particular risk in a study is actually minimal. Some comments express concern that IRBs might inappropriately grant waivers for clinical investigations that are greater than minimal risk, or that they may fail to appreciate both the nature and risks of procedures in the research studies that are submitted to them for review. Other comments caution that IRB members may have conflicts of interest that could affect their interpretation of the term. To support their concerns and opposition, these comments cite past instances in which researchers had

reportedly misled subjects or inappropriately conducted research without obtaining informed consent.

Other comments suggest that additional oversight or clarification regarding IRB processes is needed with regard to granting waivers of informed consent and the determination of minimal risk. One comment urges that, if waivers are allowed, the Agency revise the proposal to address the following: clarify the process to determine whether to grant and approve waivers of informed consent, require ongoing review of waivers to determine whether IRBs are properly defining the studies as minimal risk, immediately terminate any research in which medical interventions are withheld or are too aggressive, and provide a ''whistleblower form'' for individuals involved in a research study to anonymously submit a complaint about that study to HHS. Another comment requests that FDA provide details about the practical application of the proposal, that is, how an IRB's process of determining whether to grant waivers of informed consent might work to remove the risk of variability in when and how such waivers are granted.

Some comments express concern that studies involving records or data are often labeled as minimal risk, even though IRBs struggle to make determinations about the magnitude of the risks posed by such studies and whether the risks are indeed minimal. One of these comments notes that the ability to link various sources of personal data may create additional risks for study subjects. One comment indicates concern that, in research involving real-world data (RWD) or review of health records that is categorized as ''minimal risk,'' hacking or inadvertent sharing could put the subjects' information at risk or cause subjects to be at risk for losing healthcare coverage.

(Response 10) FDA is not revising the definition of minimal risk in this rule. Retaining the current definition of minimal risk will avoid confusion in the research community and maintain harmonization with the revised Common Rule. The Common Rule and FDA regulations have shared the same definition of minimal risk since 1991,[6] and the definition of minimal risk was not changed in the revised Common Rule. Because of the longstanding consistency in the definitions of minimal risk provided in both FDA regulations and the Common Rule, IRBs have experience in applying the term ''minimal risk'' to research involving human subjects, including determining when a clinical investigation involves no more than minimal risk. Without additional detail, it is not possible to determine whether the specific types of studies the comments identify as minimal risk would involve no more than minimal risk to the subjects (see also response to Comment 19). However, we agree with these comments' support for waiving or altering informed consent to facilitate minimal risk research that meets the requirements of § 50.22.

In response to comments suggesting that IRB members might have conflicts of interest that could affect their interpretation of the term ''minimal risk,'' we note that IRBs are subject to the requirements under § 56.107 (21 CFR 56.107), including the requirements prohibiting participation in IRB review by a member with a conflict of interest, except to provide information requested by the IRB, under § 56.107(e).

With respect to the comment that recommends revising the rule to clarify the process of an IRB waiver determination and require ongoing review for waivers to determine the adequacy of IRBs' interpretation of ''minimal risk,'' we note that IRBs are required to prepare and follow written procedures for conducting reviews of FDA-regulated clinical investigations (see 21 CFR 56.108(a) and 56.115(a)(6)). These written procedures should include an IRB's processes for reviewing requests to waive or alter informed consent and documenting that the criteria in § 50.22 are satisfied. We also note that FDA inspects IRBs to determine whether they are reviewing and approving research in accordance with FDA regulations and with the IRBs' written procedures. We do not believe it is necessary to prescribe a particular process or procedure that IRBs must follow when making and documenting a waiver or alteration decision for a research study, or that such a process would result in more consistent decision making. FDA regulations provide for flexibility in terms of the specific contents of IRB written procedures, which gives IRBs the ability to establish procedures best suited to their own operations. Written procedures, including the processes IRBs follow for making certain determinations, may vary among institutions and IRBs because of differences in the way organizations are structured, the type of research studies reviewed by the IRB, institutional policy or administrative practices, the number of IRBs at the institution, affiliation with an institution, or local and State laws and regulations (Ref. 8).

FDA also declines the commenter's suggestion to add to the rule a requirement that research be terminated that withholds or provides for aggressive medical intervention. Although the comment does not elaborate on the meaning of an ''aggressive'' medical intervention, it does not appear that the types of research studies the comment describes would qualify for a waiver or alteration under § 50.22. In addition, if changes are proposed to a study for which a waiver or alteration has been granted under § 50.22, and those changes include the addition of an investigational intervention or other protocol amendment that involves more than minimal risk to subjects, then the study, with the change, would no longer qualify for the waiver or alteration.[7] With regard to the comment encouraging a process for HHS to receive anonymous complaints from individuals involved in a research study, FDA notes these processes are already in place for both FDA [8] and HHS.[9]

Regarding the comment suggesting that hacking or inadvertent sharing of health information can create risks for subjects, such as losing healthcare coverage, we note that § 56.111(a)(7) (21 CFR 56.111(a)(7)) of FDA's regulations requires IRBs to determine that, where appropriate, adequate provisions to protect subjects' privacy and maintain the confidentiality of data are in place in order to approve FDA-regulated research. This would include research for which the IRB grants a waiver or alteration of consent under § 50.22.

As previously noted, FDA plans to publish guidance to assist IRBs in applying the criteria for waiver or alteration of informed consent requirements in § 50.22 to FDA-regulated clinical investigations. In that guidance, we intend to include additional information on the types of research activities that may involve no

[6] 83 FR 57378 at 53781.

[7] While outside the scope of this rulemaking, FDA's existing IRB regulations at 21 CFR 56.113 provide for termination of IRB approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

[8] Complaints related to FDA-regulated clinical investigations should be reported to the Center responsible for the product involved. Additional information and contact information for each Center is available at: *https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/reporting-complaints-related-fda-regulated-clinical-trials.*

[9] Complaints related to research subject to HHS regulations may be emailed to OHRP's Director of the Division of Compliance Oversight at *complaints.ohrp@hhs.gov*. More information is available at: *https://www.hhs.gov/ohrp/compliance-and-reporting/submitting-a-complaint/index.html.*

more than minimal risk to the subjects and therefore might qualify for a waiver or alteration of informed consent.

(Comment 11) One comment, focused on device studies, warns about the potential for confusion and inconsistent interpretation across IRBs when applying the concept of ''minimal risk'' to studies of ''non-significant risk'' devices.

(Response 11) FDA addressed the difference between ''non-significant risk'' and ''minimal risk'' in a 2006 guidance for IRBs, clinical investigators, and sponsors entitled ''Significant Risk and Nonsignificant Risk Medical Device Studies'' (SR/NSR Guidance; Ref. 9). In the SR/NSR Guidance, FDA explains that ''non-significant risk'' and ''minimal risk'' determinations are distinct and involve different considerations. IRBs that review device investigations have experience applying FDA's regulations at parts 50, 56, and 812, and the SR/NSR Guidance has been in place for many years as a resource. As a result, IRBs should be aware that ''non-significant risk'' and ''minimal risk'' are different concepts that serve different regulatory purposes. Given this experience, we do not believe that IRBs will encounter difficulty applying the concept of ''minimal risk'' in § 50.22 to clinical investigations involving ''non-significant risk'' devices.

2. The Waiver or Alteration Will Not Adversely Affect the Rights and Welfare of the Subjects (Proposed § 50.22(b))

The proposed rule included, as the second criterion, that the waiver or alteration will not adversely affect the rights and welfare of the subjects.[10] FDA stated in the preamble of the proposed rule that, to make this finding, IRBs may consider, for example, whether the waiver or alteration has the potential to negatively affect the subjects' well-being or whether the subject population in general would likely object to a waiver or alteration being granted for the research in question (83 FR 57378 at 57381 to 57382). It would not be necessary for an IRB to find that obtaining informed consent would be harmful or contrary to the best interests of subjects in order to satisfy this criterion.

(Comment 12) Several comments mention the effects of the proposed rule on subjects' rights and welfare. Some comments oppose the idea of a waiver of consent, stating that the absence or omission of informed consent affects the rights of subjects. Two comments assert that a waiver of informed consent would be unethical and in violation of subjects' trust because subjects would be prevented from knowing who is seeing or using their records, and the waiver would take away the subjects' choice and ability to specify how their data will be used. An additional comment mirrors this concern and notes the importance of protecting personal data.

Two comments object to waiving consent on the grounds that doing so would deny subjects necessary information about the research (*e.g.,* the name of the sponsor, a description of the research or research protocol, a description of subjects' rights, who to contact in the event of injury) and would deny subjects the right to object to participation in the research, the right to withdraw from the research, and the right to recourse and remedy in the event of issues or wrongdoing. Finally, one comment objects to the rule based, in part, on a lack of definitions for the term ''welfare'' and the phrase ''welfare of the subjects.''

(Response 12) FDA does not agree with the comments suggesting that allowing for a waiver of informed consent for minimal risk clinical investigations in the circumstances described in § 50.22, including the criterion in proposed § 50.22(b), adversely affects the rights of subjects or is unethical or in violation of subjects' trust. We note that provisions relating to safeguarding the rights and welfare of subjects in clinical investigations have been included in FDA's regulations for decades. Section 56.107(a) of our regulations on IRB membership requires that each IRB be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. We believe that an IRB responsible for the review, approval, and continuing review of a minimal risk clinical investigation that meets these membership requirements is capable of finding and documenting, as appropriate, that the waiver or alteration will not adversely affect the rights and welfare of subjects participating in the research. Additionally, we note that to approve a clinical investigation, including a clinical investigation for which informed consent is waived or altered under this rule, an IRB must find that, where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (§ 56.111(a)(7)).

We believe that the safeguards in § 50.22 also help to alleviate the comments' concerns regarding subjects' access to information about the research, as we anticipate that IRBs will consider if any study information falling within the elements listed in § 50.25(a) or (b) should be provided to subjects. If so, the IRB may conclude, for example, that an alteration of certain informed consent elements is appropriate rather than a waiver, or that it is appropriate for the subjects or their LARs to be provided with additional pertinent information after participation (see § 50.22(e) in this rule).

In response to the comments objecting to the waiver provision as unethical or adversely affecting subjects' rights, we also point to our response to comment 2 for discussion regarding the ethical principles associated with clinical research (*e.g.,* autonomy, beneficence, justice) in the context of this rule. For those FDA-regulated clinical investigations that would meet the criteria for waiver or alteration of consent under § 50.22, we believe that the protections in place under this rule are appropriate to protect the rights, safety, and welfare of human subjects while facilitating research to advance public health.

Finally, FDA declines to include a definition of ''welfare'' or ''welfare of the subjects'' in the final rule. We note that the language of ''rights and welfare of human subjects'' has a long history of inclusion in both FDA regulations for human subject protections and the Common Rule. This and similar language are also used in other well-established guidelines on human subject research (Refs. 10 and 11). Given this history, FDA believes that IRBs are accustomed to applying the term ''welfare'' to different types of research, including minimal risk research.

FDA notes that there are resources available to IRBs and the research community more broadly when considering human subject welfare in minimal risk research. For example, the Secretary's Advisory Committee on Human Research Protections (SACHRP), through its Subcommittee on Subpart A, developed several recommendations regarding the interpretation of the Common Rule criteria for a waiver or alteration of informed consent, including the criterion regarding the ''rights and welfare'' of subjects (Ref. 2).

3. The Clinical Investigation Could Not Practicably Be Carried Out Without the Waiver or Alteration (Proposed § 50.22(c))

The proposed rule included, as the third criterion, that the clinical investigation could not practicably be carried out without the waiver or

[10] We note that, in the final rule, proposed § 50.22(b) is now § 50.22(d).

alteration.[11] In the preamble to the proposed rule, FDA stated that, if scientifically sound research can practicably be carried out using only consenting subjects, FDA believes it should be carried out without involving nonconsenting subjects. FDA also provided an example of what practicable means (*i.e.,* (1) that recruitment of consenting subjects does not bias the science and the science is no less rigorous as a result of restricting it to consenting subjects or (2) that the research is not unduly delayed by restricting it to consenting subjects) (83 FR 57378 at 57382). As noted in our response to comment 7, the emphasis is on situations where it is impracticable to carry out the clinical investigation, as designed, without the waiver or alteration, rather than on situations where it is not feasible to obtain informed consent from subjects.

(Comment 13) Several comments on the proposal make reference to proposed § 50.22(c) or commented on the term ''practicably'' in this criterion. Several of the comments ask for clarification or additional guidance about the meaning of the term ''practicably'' in the proposed criterion.

One comment asserts that there is wide variation in the way IRBs interpret the practicability standard. The comment continues that some IRBs interpret impracticable to mean that the research is impossible to do with consent, while other IRBs might accept investigator resistance to obtaining informed consent as meeting the impracticability threshold. This comment also recommends that practicability determinations be made in the context of understanding the value or importance of the research, and that ''impracticable'' should be understood to mean that the burdens of getting consent are too high, given the benefit, or value, promised by the research. This comment is one of two recommending that FDA revise its interpretation of ''practicable'' to align with recommendations made by SACHRP in 2008 related to waiver of informed consent and interpretation of minimal risk under the Common Rule (Ref. 2).

Another comment seeks reassurance that one of the objectives of § 50.22 is to provide IRBs with the latitude to allow a sponsor to have access to and utilize data and/or biospecimens that have already been collected without having to obtain informed consent. The comment encourages the inclusion of examples of minimal risk investigations to help IRBs understand that they have the flexibility to make real-world assessments of whether the research would be rendered impracticable because of the unavailability of subjects to give new individual consent.

A final comment asks that FDA clarify the meaning of the phrase ''unduly delayed'' in its description of the term ''practicable.'' This comment states that more effort should be put into finding an alternative to conducting research without subjects' consent.

(Response 13) With respect to the interpretation of the term ''practicably,'' we reiterate that the emphasis is on situations where it is impracticable—not necessarily impossible—to carry out the clinical investigation, as designed, without the waiver or alteration. Practicability should be assessed on a case-by-case basis considering the unique factors associated with the clinical investigation, such as its aims, its population(s), and the impact on its scientific validity if informed consent were required (*e.g.,* introduction of bias). The relevant considerations, and the weight given to each consideration, should reflect the unique circumstances of the clinical investigation for which a waiver or alteration of informed consent is being sought.

If an IRB finds that a clinical investigation can be practicably carried out using only consenting subjects, then FDA believes it should be carried out without involving nonconsenting subjects. However, we agree that, under this final rule, an IRB can approve a clinical investigation falling within the scope of part 50 in which investigators will have access to and utilize data and/or biospecimens that have already been collected without having to obtain informed consent, provided the IRB finds and documents that the criteria under § 50.22 are met.

In addition, we agree that IRBs may find under § 50.22(b) (§ 50.22(c) in the proposed rule) that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent based on the unavailability of certain subjects in an investigation to give consent for a new investigation (*e.g.,* subjects lost to followup), when restricting the research to the subjects available to provide consent would compromise the scientific or ethical integrity, or cause undue delay of, the investigation.

As some comments point out, SACHRP made recommendations in 2008 related to waivers of informed consent and the interpretation of minimal risk under the Common Rule, including the Common Rule waiver criterion that corresponds to § 50.22(b). In its recommendations, SACHRP emphasized that the criterion ''states that the research could not practicably be carried out without the waiver or alteration. Put another way, it would not be practicable to perform the research (as it has been defined in the protocol by its specific aims and objectives) if consent was required'' (Ref. 2). SACHRP also offered the following concepts to help an IRB determine whether the research could not be practicably carried out without the waiver or alteration of consent: (1) the scientific validity of the research would be compromised if consent were required; (2) ethical concerns would be raised if consent were required; (3) there is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained; and (4) practicability should not be determined solely by considerations of convenience, cost, or speed.

Although SACHRP's recommendations regarding the ''practicably'' waiver criterion were developed for research that is regulated under the Common Rule, they are consistent with FDA's interpretation of the corresponding waiver criterion in this rule (*i.e.,* § 50.22(b)). It thus may be appropriate for an IRB to find that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent on the grounds that ethical concerns would be raised if consent were required (*e.g.,* an investigation using previously collected biospecimens where obtaining subjects' consent for secondary research use of the biospecimens may expose individuals to new privacy risks by linking the biospecimens with nominal identifiers in order to contact the individuals to seek consent). In some cases, these ethical concerns could justify a finding of impracticability under § 50.22(b) even if the scientific validity of the clinical investigation would not be compromised by asking the individuals to provide informed consent.

In addition, as stated in the preamble to the proposed rule, FDA interprets the term ''practicably'' in § 50.22(b) to mean, for example, that the research is not unduly delayed by restricting it to consenting subjects (83 FR 57378 at 57382). The phrase ''unduly delayed'' refers to more than just considerations of speed. By ''unduly delayed,'' we mean a delay in the initiation of a clinical investigation that is so lengthy as to raise ethical or scientific concerns given the benefit, or value, potentially gained by the research (*e.g.,* delaying the initiation of an investigation of a rare disease treatment by several years in

[11] We note that, in the final rule, proposed § 50.22(c) is now § 50.22(b).

order to allow for collection of new biospecimens from consenting subjects with the rare disease, when biospecimens from individuals with the disease are available from a repository but the biospecimens have no accompanying current contact information). Accordingly, an IRB may make a finding that the research could not practicably be carried out without the requested waiver or alteration because requiring consent would unduly delay the research.

We note that it would be inappropriate for an IRB to find that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent based solely on a clinical investigator being resistant to obtaining informed consent. We do not consider investigator resistance to obtaining informed consent to be a scientifically or ethically valid reason for finding under § 50.22(b) that a clinical investigation could not practicably be carried out without a requested waiver or alteration of informed consent.

4. Whenever Appropriate, the Subjects Will Be Provided With Additional Pertinent Information After Participation (Proposed § 50.22(d))

As the fourth criterion, FDA proposed that, whenever appropriate, the subjects will be provided with additional pertinent information after participation.[12] For example, an IRB may find that information that had been previously withheld about the clinical investigation to prevent bias must be provided to subjects following their participation.

(Comment 14) FDA received a few comments about proposed § 50.22(d). Two comments cite a lack of clarity about the phrase ''whenever appropriate'' and one asks ''when and why'' it would not be appropriate to provide a subject with pertinent information after the research has ended. One comment recommends that definitions for § 50.22(d) be included, without providing further specificity on the definitions to be included.

(Response 14) For this criterion, the phrase ''whenever appropriate'' means that, when evaluating whether this criterion is met, the reviewing IRB considers factors relevant to the specific clinical investigation and population of the study under review to determine whether an investigator should provide information to the subjects of the minimal risk clinical investigation or to their LARs after participation (Ref. 2). One example where providing additional pertinent information after participation may be appropriate is in the case where some aspects of the study are not fully disclosed upfront because full disclosure may interfere with the purpose of the study (*e.g.,* full knowledge might cause subjects to act differently than they naturally would during the study). In that case, withholding full information upfront helps to ensure subject responses are not biased. Providing subjects with additional pertinent information about the study after participation may be appropriate.

FDA declines the recommendation that definitions in § 50.22(d) be included, as we do not have additional information from the commenter regarding what specific definitions should be described. As noted in our responses to comments 6 and 10, we believe that IRBs are equipped to consider the criteria outlined in the rule, as IRBs have experience applying the criteria in the corresponding Common Rule provision for waiver or alteration of informed consent. IRBs also have resources available to draw upon when considering a waiver or alteration of informed consent for minimal risk research (Ref. 2).

D. Comments on Adopting the Revised Common Rule's Fifth Criterion for Waiver or Alteration of Informed Consent

In the proposed rule, FDA explained that the revised Common Rule retained the same four criteria for IRB waiver or alteration of informed consent as were included in the 1991 version of the Common Rule, but added a fifth criterion, *i.e.,* ''if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format'' (45 CFR 46.116(f)(3)(iii)). FDA proposed to adopt the four criteria from the 1991 version of the Common Rule but did not propose to adopt the fifth criterion at that time. Instead, FDA invited public comment on whether to include the fifth criterion in FDA regulations.

(Comment 15) Several comments support including the fifth criterion in the final rule because it would harmonize FDA's criteria in § 50.22 for a waiver or alteration of informed consent for minimal risk clinical investigations with the revised Common Rule's criteria in 45 CFR 46.116(f)(3) and would support the continued protection of human subjects by addressing identifiable private information and biospecimens. Some comments also note that adopting the fifth criterion is consistent with the goal of reducing administrative burden. One comment expresses the concern that less than complete harmonization would do nothing to reduce the time and effort spent training staff and developing multiple sets of forms and processes for review of research under different standards.

Some comments maintain that inclusion of the fifth criterion is helpful because research involving biospecimens is an area of confusion and controversy and including the fifth criterion provides clarification of FDA's policy. One comment asserts that omission of the fifth criterion would contribute to the mistaken belief that FDA's regulations do not permit a waiver or alteration of informed consent for minimal risk research involving identifiable biospecimens.

Two comments request FDA's rationale for not promulgating the fifth criterion if the criterion is not adopted in the final rule. Another comment recommends that FDA revise the definition of human subject at § 50.3(g) to clarify the applicability of part 50 to private information and biospecimens. This comment also recommends that, given that ''identifiability is more fluid than the term implies, and technology is rapidly changing how data can be identified,'' FDA adopt a provision, similar to the revised Common Rule at 45 CFR 46.102(e)(7), requiring the Agency to periodically reevaluate the meaning of ''identifiable'' and what technologies or techniques generate identifiable information or specimens.

(Response 15) FDA is adopting the fifth criterion in this final rule. To match the structure of the revised Common Rule's general waiver provision (*i.e.,* 45 CFR 46.116(f)), the fifth criterion has been incorporated into the codified text at § 50.22(c).

In adopting the fifth criterion, we are harmonizing the waiver criteria set forth in § 50.22 with those set forth in the revised Common Rule's general waiver provision (45 CFR 46.116(f)(3)). As discussed in our response to comment 1, we expect that this harmonization will reduce administrative burdens on IRBs and researchers and reduce research costs. We also agree with comments noting that inclusion of the fifth criterion in the codified text will help avoid confusion regarding the applicability of § 50.22 to minimal risk clinical investigations involving the use of private information or biospecimens in an identifiable format. The fifth criterion makes it clear that § 50.22 applies to minimal risk clinical investigations involving the use of

[12] We note that, in the final rule, proposed § 50.22(d), as revised, is now § 50.22(e).

identifiable private information or identifiable biospecimens and that IRBs are permitted to waive or alter informed consent for such investigations, provided the IRB finds and documents that the other criteria in § 50.22 are met and that the investigation could not practicably be carried out without using such information or biospecimens in an identifiable format.

We decline the recommendation to revise the definition of ''human subject'' in § 50.3(g), as changes to the definition of ''human subject'' could have unintended effects on other sections in part 50 beyond the scope of this rule. We also decline to adopt a provision that would require FDA to periodically reexamine the definitions of ''identifiable private information'' or ''identifiable biospecimen.'' We note that definitions of ''identifiable private information'' and ''identifiable biospecimen'' are included in FDA's proposed rule to amend part 50, Protection of Human Subjects, and part 56, Institutional Review Boards (87 FR 58733, September 28, 2022). Additionally, the revised Common Rule includes provisions at 45 CFR 46.102(e)(7)(i) and 46.102(e)(7)(ii) that require Federal departments and Agencies implementing the revised Common Rule, regularly and upon consultation with appropriate experts, to (i) reexamine the meaning of ''identifiable private information'' and ''identifiable biospecimen'' [13] and (ii) assess whether there are analytic technologies or techniques that should be considered to generate identifiable private information or identifiable biospecimens. FDA intends to participate in these efforts with HHS and the other Federal departments and Agencies, providing input on FDA-regulated research and promoting consistent and appropriate interpretation of these terms across HHS and FDA human subject research regulations. Including a new requirement in FDA's regulations for FDA to consider issues relating to the meaning of ''identifiable,'' on a periodic basis and in light of evolving technology, is thus unnecessary and could result in duplicative efforts and additional burden on the Agency without added benefit.

(Comment 16) A few comments oppose adopting the fifth criterion. Two comments observe that FDA did not propose to establish a regulatory definition for ''identifiable.'' These comments assert that the definitions of the terms ''identifiable private information'' and ''identifiable biospecimen'' in the revised Common Rule must be periodically reevaluated under 45 CFR 46.102(e)(7) and may change in the future, which could impact research involving identifiable biospecimens and identifiable private information in unknown ways. In addition, these comments maintain that the fifth criterion could lead to unintended negative consequences, such as investigators being reluctant to retain identifiers needed for quality control purposes and for the verification of data that may be required for FDA submissions, applications, and approvals. The comments also express concern that IRBs may be reluctant to grant waivers for research with identifiable biospecimens and data. Additional comments contend that the fifth criterion is unnecessary because it does not provide additional human subject protections beyond those provided by the other criteria in proposed § 50.22, or because certain types of research (*i.e.,* on biospecimens) fall outside the scope of FDA-regulated clinical investigations because the research does not include a ''human subject.'' Finally, one comment asserts that informed consent should never be waived for research involving identifiable private information or biospecimens.

(Response 16) FDA declines to add a definition for ''identifiable'' in this rule. As noted in our response to comment 15, we include definitions of ''identifiable private information'' and ''identifiable biospecimen'' as part of our proposed rule to amend part 50, Protection of Human Subjects, and part 56, Institutional Review Boards. In that rule, the proposed definitions of ''identifiable private information'' and ''identifiable biospecimen'' harmonize with the revised Common Rule's definitions of these terms (45 CFR 46.102(e)(5) and (6)).

With respect to the revised Common Rule definitions for ''identifiable private information'' and ''identifiable biospecimen,'' we acknowledge that the meaning of these terms must be periodically reexamined pursuant to 45 CFR 46.102(e)(7) and that they may be interpreted differently by the Common Rule departments and Agencies in the future. However, we believe the commenters' concerns regarding the potential impact on FDA-regulated research of such periodic reexaminations can be addressed through FDA's involvement in the consultation process described in the revised Common Rule, as discussed in the response to comment 15. Additionally, these comments do not provide a basis for us to conclude that adoption of the fifth criterion will have unintended negative consequences for investigator retention of identifiers. We fully expect clinical investigators to retain the identifiers for private information and biospecimens when it is necessary to do so for quality control purposes. A failure to preserve the identifiers could compromise the integrity of an investigation's results. We do not believe clinical investigators will risk compromising an investigation to avoid triggering the fifth criterion in any research involving private information or biospecimens. Nor are we aware of evidence that IRBs will be reluctant to waive or alter informed consent for clinical investigations involving private information or biospecimens in an identifiable format when the waiver criteria are met, or that IRBs are more reluctant to waive informed consent for research involving identifiable private information or biospecimens since the fifth criterion has been adopted in the revised Common Rule. FDA expects IRBs to evaluate carefully each request and grant a waiver or alteration of informed consent only when adequately justified.

We disagree with the contention that the fifth criterion is unnecessary because it does not provide additional human subject protections beyond what the other criteria provide. The fifth criterion respects subjects' interests in protecting the confidentiality of their information and biospecimens by embodying the principle that nonidentifiable private information and nonidentifiable biospecimens should be used whenever possible in clinical investigations for which informed consent is not obtained.[14] Although some IRBs might consider these privacy interests as a part of analyzing other criteria in § 50.22, the fifth criterion requires that all IRBs consider these interests when determining whether to grant a waiver or alteration of informed consent under § 50.22 for a clinical investigation involving identifiable

[13] The provision in 45 CFR 46.102(e)(7)(i) further provides that, if appropriate and permitted by law, these Federal departments and Agencies may alter the interpretation of these terms, including through the use of guidance.

[14] In adopting this criterion, the preamble to the revised Common Rule stated: ''This criterion was modeled on the comparable criterion in the HIPAA Privacy Rule, which requires as a condition of waiver of the requirement to obtain an individual's authorization that the research could not practicably be conducted without access to and use of protected health information. The principle embodied in this additional proposed criterion was that nonidentified information should be used whenever possible in order to respect subjects' interests in protecting the confidentiality of their data and biospecimens'' (see 82 FR 7149 at 7224).

private information or identifiable biospecimens.

In response to the comment suggesting that the fifth criterion is unnecessary because ''biospecimen research'' does not involve a human subject and thus does not meet the definition of ''clinical investigation,'' we disagree. The comment points to FDA's definition of ''human subject'' in § 50.3(g) (''*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.''). We note that FDA's existing IDE regulations (§ 812.3(p)) refer specifically to specimens in the definition of ''subject'' (*i.e.,* ''*Subject* means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control.''). FDA's IDE regulations cross-reference part 50 with respect to requirements for obtaining informed consent (see, *e.g.,* §§ 812.2(b)(1)(iii) and 812.100), and the Agency's longstanding position is that FDA-regulated device investigations using biospecimens are subject to informed consent requirements under part 50 (Refs. 12 and 13). Additionally, as the comment itself subsequently points out, the inclusion of this criterion may be helpful to biospecimen research by providing clarity on this issue.

We also do not agree that informed consent should never be waived for clinical investigations involving private information or biospecimens in an identifiable format. Such research plays an important role in the discovery and development of innovative medical products, and it may not be practicable to perform the research if investigators are required to obtain informed consent from the individuals associated with the private information or biospecimens. Without the possibility of a waiver of informed consent, scientific progress in many therapeutic areas could be slowed. We believe that the criteria for obtaining a waiver or alteration of informed consent in § 50.22 (including, for example, that ''[t]he waiver or alteration will not adversely affect the rights and welfare of the subjects''), in conjunction with the requirement in § 56.111(a)(7) that requires IRBs, in order to approve research, to determine that ''[w]here appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data,'' adequately protect the privacy of individuals while not unduly inhibiting research that could benefit the public health.

E. Comments on Secondary Research Involving Leftover Biospecimens

A few public comments address the applicability of § 50.22 to secondary research involving previously collected human biospecimens.

(Comment 17) One comment points out that FDA has an existing policy, the ''Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable'' (Leftover Specimen Guidance; Ref. 12), that addresses the use, without informed consent, of nonidentifiable leftover human specimens in certain in vitro diagnostic (IVD) device investigations. This comment recommends incorporating key elements of section IV of the Leftover Specimen Guidance into § 50.22(a) to clarify when IRBs may waive informed consent for IVD device investigations that use nonidentifiable leftover human specimens. The comment specifically proposes adding a new paragraph to § 50.22(a) that would identify IVD device investigations meeting these key elements as examples of clinical investigations that involve no more than minimal risk to subjects.

(Response 17) We decline the commenter's suggestion to add a new paragraph to § 50.22(a) that would include key elements of section IV of the Leftover Specimen Guidance as examples of clinical investigations that involve no more than minimal risk to the subjects because such a change would create unnecessary differences between the revised Common Rule's general waiver provision (*i.e.,* 45 CFR 46.116(f)) and § 50.22. Such differences could cause confusion for IRBs that review and approve clinical research under both sets of regulations.

We believe that most IVD device investigations falling within the scope of the policy described in section IV of the Leftover Specimen Guidance will satisfy the criteria at § 50.22. However, to the extent that there are IVD device investigations that fall within the scope of the Leftover Specimen Guidance but do not satisfy the waiver criteria in § 50.22, FDA is retaining the Leftover Specimen Guidance at this time to help avoid potential disruption to IVD device investigations as IRBs gain experience implementing the new waiver provision in § 50.22 for FDA-regulated clinical investigations.

(Comment 18) Two comments support the proposal, noting that it would facilitate research on residual biospecimens (*e.g.,* archived pathology biospecimens) that is critical for developing new biomarkers for use in diagnosing and measuring the progress of disease in a patient. These comments remark that seeking informed consent retrospectively from the patients from whom the biospecimens and related clinical data were obtained during the course of routine care or for other research purposes may be very difficult or even impossible because, for example, the patients cannot be located. Both comments note that FDA recognized the challenges that obtaining informed consent can pose for secondary biospecimen research in the Leftover Specimen Guidance, which indicates that FDA intends to exercise enforcement discretion with regard to the use, without informed consent, of leftover biospecimens in IVD device studies in certain circumstances. However, the comments assert that the guidance does not go far enough because it is only guidance and it does not apply to minimal risk secondary research use of biospecimens that are individually identifiable.

(Response 18) FDA agrees that clinical investigations involving the use, without informed consent, of previously collected biospecimens and related clinical data can play an important role in the development of new medical products, provided that the rights, safety, and welfare of the subjects from whom the data and/or biospecimens were obtained are adequately protected. For example, leftover biospecimens are frequently used in feasibility studies and studies to characterize the performance of new IVD devices. In addition, banked leftover biospecimens can be a source for unique and possibly rare specimens in sufficient quantity to permit the rapid completion of IVD device investigations that would be very difficult to conduct in a reasonable timeframe without these specimens. This rule addresses the minimal risk secondary research use of biospecimens that are individually identifiable by permitting IRBs to waive or alter informed consent for a clinical investigation involving the use of such specimens if they find and document that the waiver criteria in § 50.22 have been satisfied.

F. Comments on Examples of Clinical Investigations That Would Meet the Waiver Criteria

In the proposed rule, FDA solicited additional public input on the types of FDA-regulated clinical investigations for which sponsors would anticipate requesting a waiver or alteration of informed consent from the IRB. Several respondents provide examples of the types of studies for which sponsors would anticipate requesting a waiver or alteration of informed consent.

(Comment 19) Several comments provide the example of secondary research on biospecimens, *e.g.,* studies using leftover identifiable and/or non-identifiable human biospecimens, as the type of minimal risk clinical investigations for which sponsors would anticipate requesting a waiver or alteration of informed consent from the IRB.

One comment provides the hypothetical example of an investigator who wants to use archived prostate cancer biospecimens and clinical data for a study of a new molecular marker of response to treatment for which the investigator anticipates submitting an application to FDA. The comment includes the caveat that the investigator could use the archived biospecimens with 10 years of clinical data but for the ability to obtain informed consent from patients. The comment concludes that, while this kind of research would offer tremendous potential to advance medical care, it would not be possible under the existing FDA regulations. The comment cites this study as an example of the type of study that would be appropriate for a waiver of informed consent under the proposed rule.

Several comments suggest that studies including RWD would exemplify of the type of studies that would benefit from the proposed regulations. One comment describes several examples of minimal risk research including RWD, such as: (1) minimal risk studies that involve previously collected biospecimens and/or data from prior studies, with the safeguard that subjects' personal data must remain protected from public disclosure; retrospective or prospective use of de-identified subject data collected in registries (*e.g.,* nested studies supplementing registry data); (2) use of de-identified electronic health record, claims, or provider data in analyses of RWD; and (3) studies using residual de-identified biospecimens collected during routine clinical practice. This comment also suggests that FDA state that consent can be waived or modified in postapproval studies (including registries) where the only research activity is the collection of anonymized standard-of-care data from subjects' medical records.

One comment provides an example of ''minimal risk emergency research'' that does not hold out the prospect of direct benefit to the subjects as a type of study where requesting a waiver or alteration of informed consent would be anticipated. The comment suggests that sponsors may want to study FDA-approved products where the use of the product is no more than minimal risk. As an example, this comment cites a clinical investigation for a new indication for an approved diagnostic device utilizing ultrasound for the diagnosis of lower extremity venous thromboses being studied for the detection of cerebral thromboses in an acute, pre-hospital setting, *i.e.,* immediately after head injury. The comment suggests that an approved ultrasound device could be deployed in the field (provided its use would not delay transport or adversely affect emergency care), and the data from the ultrasound device would not be used to guide clinical management of injured individuals, who would undergo definitive and proven diagnostic testing for cerebral blood clots after arrival in the hospital. The comment concludes that results from the ultrasound device could be compared to the definitive scan at a later time to determine its effectiveness in diagnosing cerebral thromboses.

Finally, several comments request that FDA provide specific examples of the types of clinical investigations intended to be covered by the rule, while one comment argues that instances in which informed consent is difficult or impossible to obtain in minimal risk clinical investigations would be rare and that many common examples used to illustrate minimal risk research are unlikely to qualify as clinical investigations.

(Response 19) FDA appreciates the efforts of those commenters responding to our request for examples of FDA-regulated clinical investigations for which sponsors would anticipate requesting a waiver or alteration of informed consent from the IRB. To the extent that the studies described in the comments would be considered FDA-regulated clinical investigations, we agree that some of the examples appear to be of the type for which we would anticipate sponsors might request a waiver or alteration of informed consent (*e.g.,* research involving previously collected data and biospecimens, certain studies involving FDA-approved or cleared products). However, we decline to state that certain types of clinical investigations will necessarily meet the criteria under § 50.22 for a waiver or alteration of informed consent. It is the responsibility of the reviewing IRB to determine, on a case-by-case basis considering the unique factors associated with the clinical investigation for which a waiver or alteration of informed consent is being sought, whether the criteria under § 50.22 are met. As previously noted, FDA plans to issue guidance with additional information on the types of FDA-regulated clinical investigations that may qualify for a waiver or alteration of informed consent under § 50.22.

(Comment 20) Several comments generally support the proposed rule, but ask FDA to place additional restrictions on, or limit the types of studies eligible for, such a waiver or alteration. Some comments suggest that the Agency place limitations on waivers or alterations of informed consent, such as limiting the duration of the research to 1 year or less or limiting the number of occurrences in which a waiver of consent can be used for any individual to one. Some of these comments also recommend precluding waivers or alterations of consent for a variety of research activities, including research involving interventions or invasive procedures, behavior modifications, the introduction of energy into the human body, and data collection from an individual's body or behavior in a private space. Two comments suggest that a notice be published in the **Federal Register** identifying the conditions under which the waiver or alteration would be applied, as well as additional information about the research such as the intended duration and number of human subjects in the study, a justification for why the waiver is appropriate for the research, a description of how the criteria in proposed § 50.22 were satisfied, and how the decision is consistent with the principles of the Belmont Report. Another comment asks that FDA limit the minimal risk research that could be considered for a waiver or alteration of informed consent to observational studies only. This comment also requests that, in order to protect the interests of participants, FDA require that notice be provided to study participants, either on an individual basis or publicly where the research is conducted, outlining the period the study was conducted, the purpose of the study, and the potential benefits of the study.

Other comments oppose permitting a waiver of informed consent for certain types of research, such as studies involving RWD and those being conducted in learning healthcare systems, use of specimens without consent, or studies in certain research populations, such as children or adults of diminished capacity.

A final comment states that waivers or alterations of informed consent should never be permitted for interventions on human subjects.

(Response 20) FDA does not agree with the comments suggesting that we limit the duration or number of studies that may be eligible for a waiver or

alteration of consent under § 50.22. Similarly, we decline to include additional restrictions in § 50.22 with respect to a waiver or alteration of informed consent for specific categories of research (*e.g.,* research involving behavior modifications or research involving RWD). We do not believe imposing such limitations or restrictions would provide additional protections for the rights, safety, and welfare of human subjects beyond those provided by the criteria listed in this rule and believe that these restrictions may serve to stifle innovation and advancements in research.

We also do not agree with the comments stating that individual or public notice should be required for every minimal risk clinical investigation conducted with a waiver of informed consent. While FDA regulations provide for community consultation and public disclosure in the context of the exception from informed consent requirements for emergency research (see § 50.24), FDA does not believe minimal risk research that is reviewed by an IRB and found to meet the criteria in § 50.22 necessitates these additional protections. However, under § 50.22(e), IRBs may find that additional pertinent information must be provided to subjects or their LARs after participation for the clinical investigation to qualify for a waiver or alteration of informed consent under § 50.22.

With regard to excluding children and adults with diminished capacity from the types of studies that may be conducted under § 50.22, we believe it is appropriate for studies with child subjects to qualify for a waiver or alteration under § 50.22 when the IRB finds and documents that the criteria in § 50.22 are satisfied. In addition to the requirements of § 50.22, other requirements in FDA's regulations are intended to ensure that the rights and welfare of child subjects are adequately protected. For example, to approve a clinical investigation involving children as subjects, the IRB must determine that the clinical investigation meets the requirements of part 50, subpart D, Additional Safeguards for Children in Clinical Investigations (see 21 CFR 50.50 and 56.109(h)). Similarly, FDA regulations at § 56.111(b) require that additional safeguards be included in studies to protect the rights and welfare of subjects likely to be vulnerable to coercion or undue influence. Further, § 56.111(a)(3) requires IRBs to make an assessment that the selection of subjects for any clinical investigation is equitable, including that the IRB ''should be particularly cognizant of the special problems of research involving vulnerable populations.''

FDA believes that IRBs can appropriately determine whether the criteria in § 50.22 are satisfied for research involving vulnerable populations, including children and adults with diminished capacity. FDA encourages IRBs to carefully consider the anticipated risks of the investigation as they might specifically affect vulnerable populations included in the proposed research when making findings regarding the ''minimal risk'' criterion in § 50.22(a).

Finally, we do not agree that a waiver or alteration of informed consent should never be allowed for interventions on human subjects as part of a minimal risk clinical investigation. We note that the definition of minimal risk included in FDA's regulations at § 50.3(k) is identical to the definition of minimal risk found in the revised Common Rule at 46 CFR 46.102(j). The current definition of minimal risk in both FDA regulations and in the revised Common Rule states that minimal risk means ''the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or *during the performance of routine physical or psychological examinations or tests*'' (emphasis added, § 50.3(k) and 45 CFR 46.102(j)). Under both FDA's regulations and the revised Common Rule, minimal risk studies that may be reviewed by an IRB through an expedited review procedure can include studies that require the collection of blood samples by finger stick, heel stick, ear stick, or venipuncture under certain conditions.[15] Thus, both the revised Common Rule and FDA's regulations allow for some interventions to the human body as part of minimal risk research; nothing in this rule changes the current paradigm. In instances where minimal risk research involves interventions to the human body, we think this rule strikes an appropriate balance between respect for persons and facilitating research.

G. Comments on Requests for Guidance

Several comments specifically request that FDA issue guidance on topics related to the proposed rule.

(Comment 21) A few comments request clarification and guidance to ensure that IRBs apply the criteria in § 50.22 appropriately and consistently. As noted above, several commenters request additional guidance to clarify the terms ''minimal risk'' and ''practicability.'' Others specifically ask for guidance on the applicability of a waiver for studies comparing the effectiveness of FDA-approved products to help IRBs understand and apply the criteria consistently.

One comment requests that detailed guidance on the types of clinical investigations that would and would not qualify for the waiver of informed consent be issued simultaneously with the final rule. This comment expresses the concern that clinical investigators will inappropriately seek, and IRBs inappropriately will grant, waivers of informed consent for clinical investigations that involve greater than minimal risk to subjects after FDA finalizes the proposed rule. The comment cites studies that, according to the comment, were inappropriately characterized as minimal risk by researchers and states that researchers have often mischaracterized the nature of their studies involving human subjects and minimized the risks of the procedures involved in the research in an effort to avoid the requirements for obtaining and documenting the informed consent of the human subjects.

One comment requests guidance on the relationship and interplay between the new waiver criterion (*i.e.,* the fifth criterion) and the minimal risk criterion and on what kind of information IRBs should seek to make the determination that research, if carried out with identifiable private information or biospecimens, qualifies as minimal risk.

(Response 21) Throughout this document we provide clarification of specific terms and phrases that are used in this rule. As discussed in section V.C, many of the terms used in § 50.22 have longstanding definitions in both the Common Rule and FDA's regulations (*e.g.,* ''minimal risk''). Therefore, FDA is not making further modifications to these terms and definitions in the final rule. We plan to issue guidance to assist IRBs in applying the criteria for waiver or alteration of informed consent requirements in § 50.22 to FDA-regulated clinical investigations. In that guidance, we intend to provide additional information on the types of FDA-regulated minimal risk clinical investigations that we anticipate would satisfy the criteria for a waiver or alteration of informed consent under § 50.22.

FDA believes that the structure of § 50.22, requiring IRBs to find and document that applicable criteria are met, provides appropriate safeguards to protect the rights, safety, and welfare of human subjects. We note that § 50.22 requires that the IRB responsible for the review, approval, and continuing review of a minimal risk clinical investigation

[15] See 63 FR 60353 at 60355.

find and document that the applicable criteria are met, not the researcher or sponsor of the clinical investigation. FDA believes that IRBs understand their obligations to review research to ensure the protection of the rights and welfare of human subjects and are capable of appropriately applying these criteria to minimal risk clinical investigations.

(Comment 22) One comment requests that FDA provide clarification or advisory text for sponsors, investigators, and IRBs to carefully consider the specific data elements to be collected as part of research to determine the applicability of the HIPAA Privacy Rule requirements.[16] This comment suggests that, although retrospective collection of anonymized data or research on anonymized biospecimens obtained in a previous research study would not typically require consent under the HIPAA Privacy Rule, many low-risk, retrospective, postmarket clinical followup studies may require collection of PHI and, therefore, may still require subject authorization under the HIPAA Privacy Rule. This comment recommends that FDA and HHS work together to determine the potential impact of the multiple consent requirements in the Common Rule, part 50, and the HIPAA Privacy Rule on the collection and use of RWD, and consider developing guidance on when privacy requirements apply.

(Response 22) FDA agrees that the protection of human subjects' privacy when participating in clinical investigations is important, including when the investigation uses data collected as part of clinical care. We note that the criteria for IRB approval of research in our current regulations at § 56.111(a)(7) require that, to approve research, IRBs determine that ''[w]here appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.'' This provision requires IRBs to review clinical investigations to ensure that appropriate privacy safeguards are in place to protect human subjects involved in FDA-regulated clinical investigations.

Applicability of the HIPAA Privacy Rule to clinical investigations covered by § 50.22 is outside the scope of this rulemaking. However, we note that the standards laid out in both the HIPAA Privacy Rule and the Common Rule have coexisted for many years. Accordingly, FDA believes that IRBs have experience considering both rules when reviewing minimal risk research. By harmonizing the waiver criteria set forth in § 50.22 with those set forth in the revised Common Rule's general waiver provision, we are promoting consistency in the application of such requirements across Common Rule Agencies and minimizing burden to IRBs tasked with applying the criteria described in this rule to FDA-regulated research.

H. Comments on the Expedited Review List and IRB Continuing Review

(Comment 23) Some comments question the interpretation of ''minimal risk'' in the proposed rule in relation to the list of categories of research that may be reviewed by the IRB through an expedited review procedure (''expedited review list,'' Ref. 14). One comment disagrees with categories of research included on the expedited review list. Another comment notes that, while the expedited review list categories could provide some benchmarks for the types of research that are minimal risk, these applications are limited and there may be research that qualifies as ''minimal risk,'' that would not qualify for the expedited review procedure.

Similarly, some comments express concern that the proposed rule did not address how FDA intends to harmonize with the revised Common Rule with respect to expedited review procedures and IRB continuing review. A few comments cite SACHRP's recommendations on the expedited review list (Ref. 15) and note concern about FDA and HHS adopting them. These comments assert that if FDA and HHS adopt the SACHRP recommendations and FDA harmonizes with changes made in the revised Common Rule regarding expedited review (*e.g.,* by permitting expedited review of research activities appearing on the expedited review list, unless the IRB reviewer determines that the studies involve more than minimal risk) would weaken human subject protections. Other comments state that human subject protections would be weakened if FDA adopts the revised Common Rule's requirement that eliminates IRB continuing review for studies that are eligible for review under an expedited review procedure. These comments urge that minimal risk studies for which an IRB waives informed consent remain subject to IRB continuing review.

(Response 23) FDA agrees with the comments to the extent they emphasize the importance of ensuring that waivers or alterations of informed consent under this rule are granted only for research that presents no more than minimal risk to the subjects. However, we do not agree that it is necessary to address how FDA intends to harmonize with the revised Common Rule's expedited and continuing review requirements as part of this rulemaking, which finalizes our proposal to permit an IRB to approve an informed consent procedure that waives or alters certain informed consent elements, or to waive the requirement to obtain informed consent, for certain minimal risk investigations. FDA issued a separate proposed rule to amend its regulations at parts 50 and 56, including with respect to expedited and continuing review (87 FR 58733), and will consider all timely comments received as part of that rulemaking, including those related to expedited review and/or continuing review. We address below the more specific concerns raised by the comments in relation to expedited or continuing review.

Some of the comments appear concerned that any changes to the FDA expedited review requirements intended to harmonize with the revised Common Rule could be perceived by the research community as broadening what qualifies as minimal risk or discourage determinations that a study presents more than minimal risk. As an initial matter, the revised Common Rule did not modify the current definition of ''minimal risk'' that is found in HHS regulations (45 CFR 46.102(j)), so FDA regulations (§ 50.3(k)) remain consistent with the definition of ''minimal risk'' provided in the revised Common Rule. In addition, under FDA's regulations at § 56.110(b)(1), for research to qualify for expedited review, a determination must be made by an IRB that the proposed research involves no more than minimal risk to human subjects. In other words, under current FDA regulations, the categories of activities appearing on the expedited review list are not presumed to be minimal risk. FDA's proposed rule to amend parts 50 and 56 (87 FR 58733) does not propose to change this. In addition, the revised Common Rule did not modify the 1998 expedited review list (63 FR 60364), so HHS and FDA (63 FR 60353) maintain identical lists of categories of research activities that may be reviewed by an IRB through the expedited review procedure. As described in the revised Common Rule, an IRB may use the expedited review procedure to review studies that involve activities appearing on the expedited review list, unless the IRB reviewer determines that the studies involve more than minimal risk (see 45 CFR 46.110(b)(1)(i)). However, OHRP has clarified that, until a new expedited review list is finalized, the entire 1998 HHS expedited review list, including the ''Applicability'' section, remains in

[16] See 45 CFR parts 160 and 164, subparts A and E.

effect for studies subject to the revised Common Rule (Ref. 16). Under the current wording of the ''Applicability'' section, to be eligible for expedited review, research must present no more than minimal risk to subjects. Therefore, for research to qualify for expedited review under the revised Common Rule, a determination must still be made by an IRB that the specific circumstances of the proposed research involve no more than minimal risk to human subjects. Under § 50.22, as finalized in this rule, an IRB must find and document that the clinical investigation involves no more than minimal risk to subjects, regardless of whether the study falls within a category on the expedited review list, to waive or alter informed consent.

As noted in comments, the revised Common Rule provision at 45 CFR 46.109(f)(1)(i) eliminates the requirement for an IRB to conduct continuing review of research that is eligible for expedited review in accordance with 45 CFR 46.110, unless the IRB determines otherwise. FDA's IRB continuing review requirements are not being revised in this rule. As explained above, FDA is engaged in separate rulemaking to amend parts 50 and 56 to harmonize with the revised Common Rule in accordance with section 3023 of the Cures Act. As part of that effort, FDA proposed changes to eliminate the requirement for an IRB to conduct continuing review of research, unless an IRB determines otherwise, that has progressed to the point that it involves only data analysis, including analysis of identifiable private information or identifiable biospecimens, and/or accessing followup clinical data from procedures that subjects would undergo as part of clinical care. However, FDA's proposed rule to amend parts 50 and 56 (87 FR 58733) does not propose to eliminate continuing review of all research eligible for expedited review, unless the IRB determines otherwise, for the reasons described in the preamble to that proposed rule. FDA will take into account the comments urging that minimal risk studies for which an IRB waives informed consent remain subject to IRB continuing review as part of finalizing any changes to continuing review requirements in that separate rulemaking.

As HHS evaluates and amends, as appropriate, its current expedited review list as required under 45 CFR 46.110(a), FDA intends to participate in the process and will update our own expedited review list, as appropriate, and will consider if any related changes to our regulations are necessary.

I. Comments on the Cost Savings of the Proposed Rule

(Comment 24) Some comments describe support for the rule because it will reduce administrative burden and result in cost savings. Other comments express the view that the proposed cost savings of the rule are low and may not outweigh the negative impact of waiving informed consent for certain minimal risk studies. One comment states that, although the potential benefits cannot be fully quantified, the analysis should focus on some of the drawbacks of this rule.

(Response 24) As discussed in section VII, FDA believes that this rule will reduce administrative burden and that any costs incurred are outweighed by non-quantifiable benefits in the form of healthcare advances resulting from research performed using a waiver or alteration of informed consent, as well as a reduction in burden for the research community arising from the harmonization of FDA's informed consent regulations with the revised Common Rule's provision for waiver or alteration of informed consent for certain minimal risk research.

However, as part of developing a response to this comment, we reanalyzed the proposed rule to consider potential additional costs associated with the rulemaking. Based on that review, we determined that there are some one-time costs associated with reading and implementing the rule, which we anticipate to be small because the final rule is harmonized with Common Rule provisions with which the clinical research community is already familiar. We also determined that there are some annual costs associated with drafting and reviewing requests for a waiver or alteration of consent. In this final rule, we include a revised analysis of cost and cost savings in the Economic Analysis of Impacts (section VII). We also determined that some of these costs are associated with collections of information subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA). For further information, see section IX.

J. Comments on the Proposed Effective Date

(Comment 25) We proposed that any final rule issued based on the proposed rule would become effective 30 days after its date of publication in the **Federal Register**. One comment requests clarification on the application of the effective date. Specifically, the comment asks whether the rule would apply only to clinical investigations that receive initial IRB approval on or after the effective date, or if it would apply to IRB review at any stage of the clinical investigation (*e.g.,* initial IRB approval or amendments) conducted on or after that date.

(Response 25) In response to this comment, we note that the rule will apply to IRB review at any stage of an FDA-regulated clinical investigation conducted on or after the effective date, including initial IRB approval or review of any changes to a previously approved clinical investigation.

VI. Effective Date

This rule is effective 30 days after the date of its publication in the **Federal Register**.

VII. 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 Regulatory Flexibility Act (5 U.S.C. 601–612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104–121), 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 Executive Order 12866 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 (5 U.S.C. 804(2)). 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 impacts, 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 final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs, Cost Savings, and Benefits

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 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 also expect that there will be cost savings to IRBs because the time burdens of reviewing waiver or alterations requests would be reduced 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 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 and that otherwise would not be conducted. We cannot quantify all benefits that might arise from such studies because of the lack of relevant data available regarding the focus of these types of studies that will support regulatory submissions to the Agency. 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 (years)	
Costs:							
Annualized Monetized millions/year							
Annualized Quantified	$1.3	$1.1	$1.8	2020	7	10	
	1.2	0.9	1.6	2020	3	10	
Qualitative							
Annualized Monetized millions/year							
Annualized	0.2	0.1	0.4	2020	7	10	
Quantified	0.2	0.1	0.4	2020	3	10	
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:							

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Docket No. FDA–2018–N–2727) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

VIII. Analysis of Environmental Impact

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

IX. Paperwork Reduction Act of 1995

In the proposed rule, FDA stated, ''This proposed rule refers to previously approved collections of information found in FDA regulations. . . . Therefore, FDA tentatively concludes the requirements in this document are not subject to additional review by OMB.'' In developing the final rule, FDA determined that there are information collections contained in the rule that are subject to review by OMB under the PRA (44 U.S.C. 3501–3521). Specifically, the final rule adds § 50.22 to part 50 to allow IRBs 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, provided the IRB finds and documents the criteria set forth in § 50.22(a)–(e). The information collections associated with part 50 have been approved in accordance with the PRA under OMB control number 0910–0130, but the additional provision at § 50.22 will modify this information collection. We estimate the rulemaking will result in an annual burden increase of 1,102 responses and 1,102 hours from recordkeeping and disclosure activity relating to the revised regulations in 21 CFR part 50.

With this exception, we conclude that the other provisions of this rule do not require substantive revisions to information collections already approved under the PRA. Provisions in part 312 (21 CFR part 312) of FDA's regulations set forth procedures for the conduct of clinical investigations of drugs and provide for the protection of human subjects involved in such investigations. Existing regulations at § 312.60 describe the general responsibilities of investigators with regard to study conduct, including ensuring the rights, safety, and welfare of human subjects. As part of these responsibilities, the current regulations require that investigators obtain informed consent, except as provided in exceptions from general requirements (§ 50.23) and exception from informed consent requirements for emergency research (§ 50.24). This final rule, as noted above, adds an additional exception to include waiver or alteration of informed consent for minimal risk clinical investigations under § 50.22. Therefore, FDA made a conforming revision to § 312.60 to cross-reference part 50 generally, rather than list each specific exception to the informed consent requirements, for simplicity and for accuracy of the cross-references in the regulatory text. FDA does not expect changes to the collections of information approved under OMB control number 0910–0014 as a result of this final rule. In addition, FDA's existing regulations at § 812.2 describe abbreviated requirements for IDEs, which require that investigators obtain and document informed consent under part 50, unless documentation is waived under IRB regulations at § 56.109(c). This final rule amends § 812.2(b)(1)(iii) to clarify that the investigator must obtain informed consent in accordance with part 50, which includes the new provision for waiver or alteration in § 50.22. The final rule also simplifies the regulatory text at § 812.2(b)(1)(iii) by removing the cross-reference to waiver of documentation of informed consent under § 56.109(c). The relevant section of the regulations in part 50 (*i.e.,* § 50.27) already refers to § 56.109(c), so the cross-reference to § 56.109(c) need not be repeated. FDA does not expect any changes to the collections of information collection approved under OMB control number 0910–0078 as a result of this final rule.

Before the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

X. Federalism

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

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

XII. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they 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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3. Executive Office of the President. Memorandum of March 27, 1997. ''Strengthened Protections for Human Subjects of Classified Research.'' 62 FR 26369 (May 13, 1997). Available at: *https://www.federalregister.gov/documents/1997/05/13/97-12699/strengthened-protections-for-human-*

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8. OHRP and FDA, ''Institutional Review Board (IRB) Written Procedures: Guidance for Institutions and IRBs'' (May 2018). Available at: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-board-irb-written-procedures.* Accessed on March 7, 2023.
9. FDA, ''Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies'' (January 2006). Available at: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.* Accessed on March 7, 2023.
10. Council for International Organizations of Medical Sciences (CIOMS), ''International Ethical Guidelines for Health-related Research Involving Humans,'' prepared by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization (2016). Available at: *https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.* Accessed on March 7, 2023.
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15. SACHRP, Recommendation to the Secretary of HHS, ''Recommendations on the Expedited Review List'' (December 12, 2017). Available at: *https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-december-12-2017/index.html.* Accessed on March 7, 2023.
16. OHRP, ''Revised Common Rule Q&As'' (December 2021). Available at: *https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html.* Accessed on March 7, 2023.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 50, 312, and 812 are amended as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

■ 1. The authority citation for part 50 is revised to read as follows:

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

■ 2. In § 50.20 revise the first sentence to read as follows:

§ 50.20 General requirements for informed consent.

Except as provided in §§ 50.22, 50.23, and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. * * *

■ 3. Add § 50.22 to subpart B to read as follows:

§ 50.22 Exception from informed consent requirements for minimal risk clinical investigations.

The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent set forth in § 50.25(a) and (b), or may waive the requirement to obtain informed consent, provided the IRB finds and documents the following:

(a) The clinical investigation involves no more than minimal risk to the subjects;

(b) The clinical investigation could not practicably be carried out without the requested waiver or alteration;

(c) If the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;

(d) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

(e) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

■ 4. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

■ 5. Revise § 312.60 to read as follows:

§ 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An

investigator shall obtain the informed consent of each human subject to whom the drug is administered, in accordance with part 50 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

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

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

■ 7. Revise § 812.2 (b)(1)(iii) to read as follows:

§ 812.2 Applicability.

* * * * *

(b) * * *

(1) * * *

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent in accordance with part 50 of this chapter.

* * * * *

Dated: December 1, 2023.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2023–27935 Filed 12–20–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Parts 3, 100, 165

[Docket Number USCG–2023–0970]

RIN 1625–AA00

Coast Guard Sector Sault Sainte Marie; Sector Name Conforming Amendment

AGENCY: Coast Guard, DHS.

ACTION: Final rule.

SUMMARY: The rule makes non-substantive changes to Coast Guard regulations in association with a change in the Coast Guard's internal organization. The purpose of this rule is to reflect that U.S. Coast Guard Sector Sault Sainte Marie has been renamed U.S. Coast Guard Sector Northern Great Lakes. This rule will have no substantive effect on the regulated public.

DATES: This rule is effective without actual notice December 21, 2023. For the purposes of enforcement, actual notice will be used from December 1, 2023, until December 21, 2023.

ADDRESSES: To view documents mentioned in this preamble as being available in the docket, go to *https://www.regulations.gov,* type USCG–2023–0970 in the search box and click ''Search.'' Next, in the Document Type column, select ''Supporting & Related Material.''

FOR FURTHER INFORMATION CONTACT: If you have questions about this rule, call or email Chief Warrant Officer Charles Palmer, U.S. Coast Guard; telephone 906–253–2462, email *Charles.b.palmer@uscg.mil.*

SUPPLEMENTARY INFORMATION:

I. Table of Abbreviations

AOR Area of responsibility
CFR Code of Federal Regulations
COTP Captain of the Port
DHS Department of Homeland Security
FR Federal Register
NPRM Notice of Proposed Rulemaking
OCMI Officer in Charge of Marine Inspections
OFCO Operating Facility Change Order
SAR Search and Rescue
§ Section
U.S.C. United States Code

II. Background Information and Regulatory History

For the last several years, the Coast Guard has sought to better align the names of its assets to correspond to the area of responsibility which they serve. Review of the missions and engagements within the northern Great Lakes region highlighted that ''Sector Sault Sainte Marie'' alone did not adequately capture the breadth and range of Coast Guard operations and relationships throughout the region. The Coast Guard has approved the name change to U.S. Coast Guard Sector Northern Great Lakes to acknowledge the long-standing commitment to all communities of the region and to reaffirm the multi-mission support that the Coast Guard provides to ensure safety at sea and enhanced maritime governance. The geographic boundaries of Sector Northern Great Lakes are not changing, and its office is not moving from Sault Sainte Marie, MI.

We did not publish a notice of proposed rulemaking (NPRM) before this final rule. The Coast Guard finds that this rule is exempt from notice and comment rulemaking requirements under 5 U.S.C. 553(b)(A) because the changes it makes are conforming amendments involving agency organization. The Coast Guard also finds good cause exists under 5 U.S.C. 553(b)(B) for not publishing an NPRM because the changes will have no substantive effect on the public and notice and comment are therefore unnecessary. For the same reasons, the Coast Guard finds good cause exists under 5 U.S.C. 553(d)(3) to make the rule effective fewer than 30 days after publication in the **Federal Register**.

III. Legal Authority and Need for Rule

The Coast Guard is issuing this rule under authority in 14 U.S.C. 504(a)(2), as delegated at 33 CFR 1.05–1(h), to issue regulations necessary to implement technical, organizational, and conforming amendments and corrections to rules, regulations, and notices.

On November 06, 2023, the Coast Guard issued Operating Facility Change Order (OFCO) No. 037–23 which changed the official unit name of U.S. Coast Guard Sector Sault Sainte Marie to U.S. Coast Guard Sector Northern Great Lakes. The previous name of Sector Sault Sainte Marie is described and reflected in regulations, which also contain contact details and other references to Sector Sault Sainte Marie. These conforming amendments update those regulations so that they contain current information.

Under 14 U.S.C. 504(a)(2), the Commandant of the Coast Guard has the authority to establish and prescribe the purpose of Coast Guard Shore establishments. This authority has been delegated to the Chief of the Coast Guard's Office of Regulations and Administrative Law under 33 CFR 1.05–1(h).

IV. Discussion of the Rule

OFCO No. 037–23, issued November 06, 2023, changed the official unit name of U.S. Coast Guard Sector Sault Sainte Marie to U.S. Coast Guard Sector Northern Great Lakes. The November 2023 OFCO did not change the area of responsibility (AOR). The AOR of U.S. Coast Guard Sector Northern Great Lakes is identical to that of what was U.S. Coast Guard Sector Sault Sainte Marie. All authorities and responsibilities previously assigned to Commander, U.S. Coast Guard Sector Sault Sainte Marie have been assigned to Commander, U.S. Coast Guard Sector Northern Great Lakes. Additionally, all authorities that were vested in the Commander, U.S. Coast Guard Sector Sault Sainte Marie as it pertains to the COTP, the OCMI, the Federal On Scene Coordinator, the Federal Maritime Security Coordinator, and the Search and Rescue Coordinator, have been assigned to Commander, U.S. Coast Guard Sector Northern Great Lakes. This rule does not change any sector, OCMI, or COTP zone boundary lines, nor does