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<AGENCY TYPE='S'>DEPARTMENT OF HEALTH AND HUMAN SERVICES

<SUBAGY>Food and Drug Administration

<CFR>21 CFR Parts 50, 312, and 812

<DEPDOC>[Docket No. FDA-2018-N-2727]

<RIN>RIN 0910-AH52

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing to amend its regulations to implement a provision of the 21st Century Cures Act (Cures Act). This proposed rule, if finalized, would allow 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 proposed rule, if finalized, would permit 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: Submit either electronic or written comments on this proposed rule by January 14, 2019.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 14, 2019. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 14, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions.")

#### *Written/Paper Submissions*

Submit written/paper submissions in the following ways:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

*Instructions:* All submissions received must include the Docket No. FDA-2018-N-2727 for “Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as

“confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule:* Janet Norden, Office of Good Clinical Practice, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-1127, or Carol Drew, Office of Good Clinical Practice, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-3505.

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### I. Executive Summary

#### *A. Purpose of the Proposed Rule*

The purpose of this proposed rule is to implement the statutory changes made to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by section 3024 of the Cures Act (Pub. L. 114-255) 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 proposed rule, if finalized, would 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 Proposed Rule*

The major provisions of the proposed rule would add § 50.22 to part 50 (21 CFR part 50) to allow IRBs responsible for the review, approval, and continuing review of clinical investigations to approve an informed consent procedure that waives or alters certain informed consent elements or that waives the requirement to obtain informed consent for certain minimal risk clinical investigations. In order for an IRB to approve a waiver or alteration of informed consent requirements for minimal risk clinical investigations, the proposed rule would require an IRB to find and document four criteria that are consistent with the “Federal Policy for the Protection of Human Subjects” (the Common Rule) (56 FR 28001, June 18, 1991). FDA believes proposed § 50.22 would provide appropriate safeguards to protect the rights, safety, and welfare of the human subjects participating in such clinical investigations. We are also proposing conforming amendments to FDA’s regulations, including § 50.20, 21 CFR 312.60, and 21 CFR 812.2.

### *C. Legal Authority*

Sections 505(i)(4) and 520(g)(3) of the FD&C Act (21 U.S.C. 355(i)(4) and 360j(g)(3)), 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 FDA’s principal legal authority for this proposed rule.

### *D. Costs and Benefits*

We do not anticipate additional costs associated with this rulemaking. This proposed rule would 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 benefits in the form of healthcare advances from such minimal risk clinical investigations and from harmonization of FDA's informed consent regulations with the Common Rule's provision for waiver of informed consent for certain minimal risk research. We cannot quantify all of these benefits because of the lack of relevant data available to FDA. The benefits that we are able to quantify are the cost savings to IRBs because the time burdens of reviewing certain minimal risk clinical investigations under differing requirements would be reduced. The estimated cost savings of the proposed rule are approximately \$237.6 thousand, with a lower bound of \$59.4 thousand and an upper bound of \$950.5 thousand. The estimated annualized costs savings of the proposed rule are approximately \$27 thousand, with a lower bound of approximately \$6,762 and an upper bound of approximately \$108.2 thousand, discounted at 3 percent over 10 years. The estimated annualized costs savings of the proposed rule are approximately \$26 thousand, with a lower bound of approximately \$6,509 and an upper bound of \$104.1 thousand, discounted at 7 percent over 10 years.

## II. Background and Description of the Proposed Regulation

### *A. Background*

On December 13, 2016, the Cures Act was signed into law, amending certain provisions of the FD&C Act. FDA is proposing to update its regulations to reflect some of those changes that are now in effect. Specifically, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) 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 proposed rule, if finalized, would implement this statutory change.

Sections 505(i) and 520(g) of the FD&C Act require FDA to publish regulations governing the use in human subjects of drugs and devices in clinical investigations. In 1962, amendments to section 505(i) of the FD&C Act provided that FDA regulations must ensure that informed consent for investigational use of drugs (including biological products) in human beings is obtained except where it is not feasible or it is contrary to the best interests of such human beings. The Medical Device Amendments of 1976 subsequently added section 520(g) to the FD&C Act. Among other requirements, section 520(g)(3)(D) of the FD&C Act directed that FDA regulations governing investigational use of devices require that informed consent be obtained except where the investigator determines in writing that there exists a life-threatening situation involving the human subject of such testing that necessitates the use of such device and it is not feasible to get the consent of the subject and there is not sufficient time to obtain such consent from the subject's representative. Section 520(g)(3)(D) of the FD&C Act further provided that a licensed physician not involved in the research must also concur in this determination, unless immediate use is necessary to save the subject's life and there is not time to get concurrence.

In 1979, FDA proposed revisions to its regulations governing informed consent (44 FR 47713, August 14, 1979). The Agency recognized in the preamble to its proposed rule that the statutory language regarding exceptions from informed consent for investigational drugs differed from that regarding investigational devices. However, the Agency explained that its prior regulations implementing the statutory exception from informed consent for investigational drugs "carefully limited" the exception to certain situations that assume "the patient subject is



seriously ill” and did not differ greatly from the new statutory exceptions from informed consent for devices (see 44 FR 47713 at 47718). When FDA issued final revisions to its informed consent regulations in 1981, it adopted a single set of requirements for informed consent for all FDA-regulated clinical investigations, which reflected the device standard in section 520(g)(3)(D) of the FD&C Act (see 46 FR 8942, January 27, 1981). FDA explained its intent to adopt a single standard that reflected the most current congressional thinking on informed consent (see 44 FR 47713 at 44718; 46 FR 8942 to 8944).

Currently, FDA’s regulations governing the protection of human subjects (21 CFR parts 50 and 56) allow exception from the general requirements of informed consent only in life-threatening situations when certain conditions are met (§ 50.23) or when the requirements for emergency research are met (§ 50.24). In all other cases, FDA regulations require that a human subject provide informed consent before participating in a clinical investigation. At this time, FDA’s regulations do not allow an exception from the general requirements of informed consent for minimal risk clinical investigations.

In contrast, the Common Rule has included waiver of informed consent provisions for minimal risk research since it was originally issued in 1991 (56 FR 28001). The Common Rule sets forth requirements for the protection of human subjects involved in research that is conducted or supported by the Department of Health and Human Services (HHS) (see 45 CFR 46, Subpart A) and 15 other Federal departments and agencies. The purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections as well as to create a uniform body of regulations across the Federal departments and agencies.<sup>1</sup> The Common Rule standard has permitted an IRB to waive the requirements to obtain informed

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<sup>1</sup> 80 FR 53931 at 53935, September 8, 2015.

consent, or to allow changes to, or omission of, some or all elements of informed consent if the IRB finds and documents that: (1) the research 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 research 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 (45 CFR 46.116(d); 56 FR 28001 at 28017).<sup>2</sup>

FDA amended its regulations in parts 50 and 56 to conform them to the Common Rule in 1991 (56 FR 28001 at 28025) but diverged from the Common Rule's provision for waiver or alteration of informed consent for minimal risk research at 45 CFR 46.116(d). In explaining the reason for this departure, FDA cited sections 505(i) and 520(g)(3)(D) of the FD&C Act<sup>3</sup> and stated that the FD&C Act "requires informed consent to be obtained from all subjects except in very limited circumstances" and that the Agency did "not have the authority under the act to waive this requirement" (53 FR 45671 at 45679, November 10, 1988).

The Common Rule provision recognizes that there may be proposed research that cannot practicably be conducted without a waiver or alteration of informed consent, but the research would contribute valuable medical or scientific knowledge and would present no more than minimal risk to subjects. FDA believes this is also true for some minimal risk FDA-regulated clinical investigations. On March 13, 2014, the Secretary's Advisory Committee on Human

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<sup>2</sup> References to the Common Rule in this document are to the 1991 version of the Common Rule, unless otherwise noted. A final rule that revised the 1991 version of the Common Rule adopted an effective and general compliance date of January 19, 2018 (82 FR 7149, January 19, 2017). On January 22, 2018, an interim final rule was published that delayed the effective and general compliance date of the revisions until July 19, 2018 (83 FR 2885). On June 19, 2018, a final rule was published that further delays the general compliance date until January 21, 2019, while allowing the use of three burden-reducing provisions for certain research during the delay period (83 FR 28497). The revised version of the Common Rule, including amendments made by the January 22, 2018 interim final rule and the June 19, 2018 final rule, is referred to in this document as the "revised Common Rule."

<sup>3</sup> FDA's proposed rule also cited section 507 of the FD&C Act, which established requirements for the conduct of clinical investigations of antibiotic drugs and provided the same exceptions from the informed consent requirements as those provided under section 505(i). Section 125 of the Food and Drug Administration Modernization Act of 1997 repealed section 507 of the FD&C Act.

Research Protections (SACHRP) considered whether the Common Rule standard for waiver of informed consent for minimal risk research would be appropriate and helpful for FDA-regulated clinical investigations. SACHRP recommended to the Secretary of HHS that FDA adopt the provisions for waiver of informed consent that existed under the Common Rule at that time at 45 CFR 46.116(d). On October 26, 2016, SACHRP reiterated that recommendation to the Secretary.<sup>4</sup>

FDA believes that the Common Rule provision has provided appropriate safeguards to protect the rights, safety, and welfare of human subjects participating in certain minimal risk research for over 25 years. Consistent with SACHRP's recommendations, FDA also believes that this standard is appropriate for FDA-regulated clinical investigations posing no more than minimal risk to human subjects. The Cures Act statutory revision authorizes FDA 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 enables FDA to harmonize with the Common Rule's well-established waiver provision for certain minimal risk research, thereby facilitating investigators' ability to conduct minimal risk clinical investigations that could contribute substantially to the development of products to diagnose or treat diseases or other conditions, without compromising subjects' rights, safety, or welfare. Because some clinical research is subject to both FDA and HHS requirements, harmonization of this waiver provision should also reduce burden on the research community.

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<sup>4</sup> SACHRP's recommendations are available at <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2014-july-3-letter-attachment-c/index.html> and <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html>.

The Common Rule was recently revised (82 FR 7149, January 19, 2017), introducing new terminology and regulatory provisions. Although it retains the same criteria for IRB waiver or alteration of informed consent as were included in the 1991 version of the Common Rule, it adds 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” (new requirement at 45 CFR 46.116(f)(3)(iii)). We are proposing to adopt the four criteria from the 1991 version of the Common Rule. At this time, we are not proposing to adopt the new fifth criterion in the revised Common Rule, which has a general compliance date of January 21, 2019; however, we invite comments on this issue. Section 3023 of the Cures Act requires the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, to harmonize the differences between the HHS human subject regulations and FDA’s human subject regulations. FDA will be working with others in HHS to carry out this statutory directive with respect to new terminology and regulatory provisions in the revised Common Rule, such as this new fifth criterion.

Subsequent to the Cures Act amendment to the FD&C Act, FDA issued a guidance document for immediate implementation, entitled “Institutional Review Board Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects” (82 FR 34535, July 25, 2017). This guidance informed 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 informed 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 regulations to implement section 3024 of the Cures Act become effective.

Obtaining informed consent from those who volunteer to participate in research is a fundamentally important principle of human subject protection. FDA is issuing this proposed rule to permit IRB waiver or alteration of informed consent in limited circumstances, consistent with the Cures Act. Given the variety and complexity of clinical investigations being conducted in today's research environment, FDA is soliciting additional stakeholder input 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.

#### *B. Description of the Proposed Regulation*

FDA proposes to add § 50.22, "Exception from informed consent requirements for minimal risk clinical investigations" to part 50. The proposed exception would allow 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 that waives the requirement to obtain informed consent, provided that the IRB finds and documents that:

- the clinical investigation involves no more than minimal risk to the subjects;
- the waiver or alteration of informed consent will not adversely affect the rights and welfare of the subjects;
- the clinical investigation could not practicably be carried out without the waiver or alteration of informed consent; and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Consistent with the amendments made by section 3024 of the Cures Act, § 50.22(a) would limit the application of a waiver or alteration of informed consent under proposed § 50.22 to clinical investigations that involve no more than minimal risk. FDA regulations and the Common Rule have shared the same definition of “minimal risk” since 1991 (see 56 FR 28025, June 18, 1991; § 50.3(k); 45 CFR 46.102(i)).<sup>5</sup>

Proposed § 50.22 also provides for appropriate safeguards to protect the rights, safety, and welfare of human subjects. Proposed § 50.22(b) requires the reviewing IRB to find that the waiver or alteration will not adversely affect the rights and welfare of the subjects. 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. 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.

Proposed § 50.22(c) requires the reviewing IRB to find that the clinical investigation could not practicably be carried out without the waiver or alteration. If scientifically sound research can be practicably carried out using only consenting subjects, FDA believes it should be carried out without involving nonconsenting subjects. By practicable, FDA means, for example: (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. 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 human subjects.

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<sup>5</sup> In the revised Common Rule, the definition of “minimal risk” is found at 45 CFR 46.102(j).

Finally, proposed § 50.22(d) requires the reviewing IRB to find that, whenever appropriate, the subjects will be provided with additional pertinent information after participation. For example, an IRB may determine that information that had been previously withheld about the clinical investigation to prevent bias must be provided to subjects following their participation.

If an IRB finds and documents the criteria set forth in proposed § 50.22(a) to (d), the proposed rule would provide for the IRB 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), or that waives the requirement to obtain informed consent. This means that an IRB may waive entirely, under proposed § 50.22, the requirement to obtain informed consent, which would constitute a waiver of all elements under § 50.25(a), (b), and (c). However, regarding an alteration to the informed consent document, the proposed rule would not permit an IRB to approve an informed consent document with an omission or alteration of the specific informed consent element set forth in § 50.25(c), which requires that a statement regarding the inclusion of clinical trial information at <https://www.ClinicalTrials.gov> be provided in informed consent documents and processes for applicable clinical trials, as defined in section 402(j)(1)(A) of the Public Health Service Act, 42 U.S.C. 282(j)(1)(A).

FDA revised its informed consent regulations to add § 50.25(c) in response to section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85, September 27, 2007). Section 801 of FDAAA amended section 505(i)(4) of the FD&C Act to direct the Secretary of HHS “to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the

Public Health Service Act.” Under proposed new § 50.22, if an IRB approved the use of a consent procedure that omitted or altered certain elements in § 50.25(a) and (b), the informed consent document and/or oral presentation provided to subjects would still need to include the statement at § 50.25(c) without alteration. As FDA has previously explained, requiring a uniform statement that cannot be altered helps to ensure that potential clinical trial participants receive a consistent and accurate message that is consistent with the intent of the statutory requirement and are directed to the specific website that contains the clinical trial databank (see 76 FR 256 at 261, January 4, 2011).

Proposed § 50.22 should not be confused with the provision of the current regulations that allows for a waiver of *documentation* of informed consent by an IRB in certain situations; the waiver for documentation of informed consent referenced in § 50.27 and found in § 56.109(c), remains unchanged.

We are also proposing three conforming amendments to §§ 50.20, 312.60, and 812.2 of our current regulations to reflect the proposed exception from informed consent for minimal risk clinical investigations. FDA is proposing to revise the introductory clause of § 50.20, General requirements of informed consent, to include reference to proposed § 50.22 as one of the limited exceptions to the general requirements for informed consent. Thus, the introductory clause to § 50.20 is proposed to read, “Except as provided in §§ 50.22, 50.23, and 50.24....”

In addition, we are proposing a conforming amendment to the second sentence in § 312.60, General responsibilities of investigators, of our current regulations on investigational new drug applications to reference part 50 generally rather than list each specific exception to the informed consent requirements in part 50. This would simplify the regulatory text and make 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 proposed § 50.22.

The remaining conforming amendment we are proposing in part 812, Investigational Device Exemptions (IDEs), § 812.2(b)(1)(iii), would make it clear that the investigator must obtain informed consent in accordance with part 50, which includes proposed § 50.22. To simplify the current regulatory text, we are proposing to remove the reference to documentation being waived under § 56.109(c), as the relevant section of the regulations in part 50 (i.e., § 50.27) refers investigators to § 56.109(c) and need not be repeated. Thus, the provision of the abbreviated requirements for IDEs in § 812.2(b)(1)(iii) would be simplified to read, “(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.”

### III. Proposed Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the *Federal Register*.

### IV. Legal Authority

Title III, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) 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. We are proposing these regulations to reflect these statutory changes to the FD&C Act, including appropriate human subject protection safeguards. Thus, sections 520(g)(3)

and 505(i)(4) 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, serve as our principal legal authority for this proposed rule.

#### V. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866. Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that the proposed rule, if finalized, is an Executive Order 13771 deregulatory action and does not require us to identify cost offsets.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would not impose new requirements on any entity and therefore has no associated compliance costs, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before

proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

#### *A. Benefits of the Proposed Rule*

The proposed rule would amend FDA’s current informed consent regulations to harmonize with the 1991 version of the Common Rule’s provision for waiver of the requirement to obtain informed consent for certain minimal risk research. We expect benefits in the form of healthcare advances stemming from additional minimal risk clinical investigations that would proceed using a waiver or alteration of informed consent, and from harmonization with the Common Rule’s provision for waiver of the requirement to obtain informed consent for certain minimal risk research. The Common Rule provision is currently used by numerous other Federal departments and agencies. Some clinical research is subject to both FDA’s regulations and the Common Rule, so harmonization of this specific waiver provision would benefit those entities that conduct, sponsor, or review certain minimal risk clinical investigations by reducing confusion and burden created by the need to comply with differing requirements.

#### *B. Cost Savings of the Proposed Rule*

The proposed rule would harmonize FDA’s informed consent regulations with the 1991 version of the Common Rule’s provision for waiver of the requirement to obtain informed consent for certain minimal risk clinical investigations. As in a previous economic analysis of the 2017 revisions to the Common Rule (Ref. 1), we attempt to quantify the effects of the

proposed rule where possible. We conducted a search for active IRBs regulated by both FDA and the Office for Human Research Protections (OHRP) in HHS in the “Office for Human Research Protections (OHRP) Database for Registered IORGs & IRBs, Approved FWAs, and Documents Received in the Last 60 Days” (Ref. 2). Using this data, we are able to determine whether an IRB is active or inactive, and whether it is regulated by FDA, OHRP, or both. We multiply the number of active IRBs by the percentage of IRBs regulated by both FDA and OHRP to yield an estimate of 2,442 active IRBs that are regulated by both FDA and OHRP ( $= 3,507 \times 0.696$ ). We expect that some of these IRBs would be affected by the proposed rule, and would experience a reduction in the time burden of determining whether to approve a waiver of the requirement to obtain informed consent for a minimal risk clinical investigation by reviewing it under a harmonized standard.<sup>6</sup> We estimate that 50 percent of affected IRBs would incur time savings from the proposed rule, with a lower bound of 25 percent of affected IRBs and an upper bound of 100 percent of affected IRBs. We estimate that for affected IRBs, cost savings would be incurred in the form of time savings to IRB administrators, IRB chairs, IRB voting members, and IRB administrative staff from evaluating a minimal risk clinical investigation under FDA’s and the Common Rule’s harmonized regulations for waiving the requirement to obtain informed consent. Based on discussion with FDA subject matter experts (Ref. 3), we estimate that the reduced time burden of the proposed rule is 30 minutes (0.5 hours), with a lower bound of 15 minutes (0.25 hours) and an upper bound of 60 minutes (1 hour).

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<sup>6</sup> As previously discussed, the revised Common Rule adds a fifth criterion to the waiver or alteration of informed consent requirements (see section II.A). Although FDA is not proposing to adopt the fifth criterion in this rulemaking, for clinical investigations subject to both the Common Rule and FDA regulations, if an IRB finds and documents that research satisfies the criteria for waiver of the requirement to obtain informed consent for minimal risk research under the revised Common Rule, then that research would also meet the standards for waiver of the requirement to obtain informed consent in FDA-regulated clinical investigations described in this proposed rule.

We draw from Bureau of Labor Statistics data to estimate hourly wage rates for IRB chairs, IRB voting members, and IRB administrative staff in 2016 dollars. Based on an economic analysis of impacts of revisions to the Common Rule (Ref. 1), we use wages for postsecondary education administrators to proxy for IRB administrator wages (Ref. 4), wages for office and administrative support workers to proxy for IRB administrative staff wages (Ref. 5), and wages for postsecondary health teachers to proxy for the wages of IRB chairs and IRB voting members (Ref. 6). We double each hourly wage to account for benefits and overhead, yielding wage rates of \$134.50 for IRB administrators ( $= \$67.25 \times 2$ ), \$35.94 for IRB administrative staff ( $= \$17.97 \times 2$ ), \$109.40 for IRB chairs ( $= \$54.70 \times 2$ ), and \$109.40 for IRB voting members ( $= \$54.70 \times 2$ ). We estimate that each of these forms of labor would experience time savings as a result of the proposed rule ranging from 15 to 60 minutes, with a central estimate of 30 minutes. We also estimate that time savings would be incurred by one IRB administrator, one IRB administrative staff, one IRB chair, and one IRB voting member. We multiply the number of active IRBs regulated by the percentage of IRBs affected by the proposed rule, the estimated reduced time burden of the proposed rule, and the sum of each IRB wage rate to yield a total estimated cost savings of approximately \$237,631 ( $= 2,442 \times 0.50 \times 0.50 \times [\$134.50 + \$109.40 + \$109.40 + \$35.94]$ ), with lower bound estimated cost savings of approximately \$59,408 ( $= 2,442 \times 0.25 \times 0.25 \times [\$134.50 + \$109.40 + \$109.40 + \$35.94]$ ) and upper bound estimated cost savings of approximately \$950,524 ( $= 2,442 \times 1 \times 1 \times [\$134.50 + \$109.40 + \$109.40 + \$35.94]$ ). The net present value of the cost savings of the proposed rule is approximately \$230.7 thousand, discounted at 3 percent, with a lower bound of approximately \$57.7 thousand and an upper bound of approximately \$922.8 thousand. The net present value of the cost savings of the proposed rule are approximately \$222.1 thousand, discounted at 7 percent,

with a lower bound of approximately \$55.5 thousand and an upper bound of approximately \$888.3 thousand. The annualized cost savings of the proposed rule are approximately \$27 thousand, discounted at 3 percent over 10 years, with a lower bound of approximately \$6,762 and an upper bound of approximately \$108.2 thousand. The annualized cost savings of the proposed rule are approximately \$26 thousand discounted at 7 percent over 10 years, with a lower bound of approximately \$6,509 and an upper bound of approximately \$104.1 thousand. The estimated cost savings of the proposed rule to IRBs are summarized in table 1.

Table 1.--Cost Savings of the Proposed Rule to IRBs

	Low	Middle	High
No. of active IRBs	3,507	3,507	3,507
Percentage of IRBs regulated by FDA and OHRP	69.6%	69.6%	69.6%
No. of active IRBs regulated by FDA and OHRP	2,442	2,442	2,442
Percentage of FDA/OHRP regulated IRBs affected by the proposed rule	25%	50%	100%
Reduced time burden of the proposed rule (hours)	0.25	0.5	1
Hourly wage, IRB administrator	\$134.50	\$134.50	\$134.50
Hourly wage, IRB chair	\$109.40	\$109.40	\$109.40
Hourly wage, IRB voting member	\$109.40	\$109.40	\$109.40
Hourly wage, IRB administrative staff	\$35.94	\$35.94	\$35.94
Total cost savings of the proposed rule	\$59,408	\$237,631	\$950,524
Net present value of the proposed rule (3%)	\$57,677	\$230,710	\$922,839
Net present value of the proposed rule (7%)	\$55,521	\$222,085	\$888,340
Annualized cost savings of the proposed rule (3%, 10 years)	\$6,762	\$27,046	\$108,185
Annualized cost savings of the proposed rule (7%, 10 years)	\$6,509	\$26,035	\$104,141

### *C. Costs of the Proposed Rule*

We do not anticipate additional costs associated with this rulemaking. This proposed rule would 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.

*D. Executive Order 13771*

Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that the proposed rule, if finalized, is deregulatory under Executive Order 13771 and does not require us to identify cost offsets.

The net present value of the cost savings of the proposed rule are approximately \$222.1 thousand, discounted at 7 percent, with a lower bound of approximately \$55.5 thousand and an upper bound of approximately \$888.3 thousand. The annualized cost savings of the proposed rule are approximately \$15,546, discounted at 7 percent on an infinite time horizon, with a lower bound of approximately \$3,886 and an upper bound of approximately \$62,184. Discounted at 3 percent, the net present value of the cost savings of the proposed rule are approximately \$230.7 thousand, with a lower bound of approximately \$57.7 thousand and an upper bound of approximately \$922.8 thousand. The annualized cost savings of the proposed rule are approximately \$6,921, discounted at 3 percent on an infinite time horizon, with a lower bound of approximately \$1,730 and an upper bound of approximately \$27,685. The estimated net cost savings under Executive Order 13771 are summarized in table 2.

Table 2.--Summary of Executive Order 13771 Net Cost Savings

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	-	-	-	-	-	-
Present Value of Cost Savings	\$222,085	\$55,521	\$888,340	\$230,710	\$57,677	\$922,839
Present Value of Net Cost Savings	\$222,085	\$55,521	\$888,340	\$230,710	\$57,677	\$922,839
Annualized Costs	-	-	-	-	-	-
Annualized Cost Savings	\$15,546	\$3,886	\$62,184	\$6,921	\$1,730	\$27,685
Annualized Net Cost Savings	\$15,546	\$3,886	\$62,184	\$6,921	\$1,730	\$27,685

## VI. 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.

## VII. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). IRB actions related to the waiver or alteration of informed consent requirements are currently approved under OMB control numbers 0910-0014, 0910-0078, 0910-0130, and 0910-0755. Therefore, FDA tentatively concludes the requirements in this document are not subject to additional review by OMB.

## VIII. Consultation and Coordination with Indian Tribal Governments

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

## IX. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies



that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

#### X. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.<EXTRACT>

1. Government Publishing Office, “Federal Policy for the Protection of Human Subjects”, 82 FR 7149 (January 19, 2017), available at: <https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>, accessed on September 20, 2017.

2. Memorandum to File, FDA summary of data analysis; HHS, “Office for Human Research Protections (OHRP) Database for Registered IORGs & IRBs, Approved FWAs, and Documents Received in Last 60 Days”, prepared by Christian Brown, FDA, September 20, 2017.

3. Memorandum to File, FDA staff meeting on the Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations rulemaking, prepared by Christian Brown, FDA, September 20, 2017, addendum August 20, 2018.

4. Bureau of Labor and Statistics, "Occupational Employment and Wages, May 2016, 11-9033 Education Administrators, Postsecondary", available at:

<https://www.bls.gov/oes/2016/may/oes119033.htm>, accessed on September 20, 2017.

5. Bureau of Labor and Statistics, "Occupational Employment and Wages, May 2016, 43-0000 Office and Administrative Support Occupations (Major Group)", available at: <https://www.bls.gov/oes/2016/may/oes430000.htm>, accessed on September 20, 2017.

6. Bureau of Labor and Statistics, "May 2016 National Occupational Employment and Wage Estimates, United States", available at:

[https://www.bls.gov/oes/2016/may/oes\\_nat.htm](https://www.bls.gov/oes/2016/may/oes_nat.htm), accessed on September 20,

2017.</EXTRACT>

<LSTSUB><HED>List of Subjects

<CFR>21 CFR Part 50

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

<CFR>21 CFR Part 312

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

<CFR>21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.</LSTSUB>

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, it is proposed that 21 CFR parts 50, 312, and 812 be amended as follows:

<PART><HED>**PART 50--PROTECTION OF HUMAN SUBJECTS**

<AMDPAR>1. The authority citation for part 50 continues to read as follows:

<AUTH><HED>Authority: <P> 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, 263b-263n.

<AMDPAR>2. In § 50.20 revise the first sentence to read as follows:

<SECTION><SECTNO>§ 50.20 <SUBJECT>**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. \* \* \*

<AMDPAR>3. Add § 50.22 to subpart B to read as follows:

<SECTION><SECTNO>§ 50.22<SUBJECT> **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 that waives 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 waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (c) The clinical investigation could not practicably be carried out without the waiver or alteration; and

(d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

**<PART><HED>PART 312--INVESTIGATIONAL NEW DRUG APPLICATION**

<AMDPAR>4. The authority citation for part 312 continues to read as follows:

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

<AMDPAR>5. Revise § 312.60 to read as follows:

**<SECTION><SECTNO>§ 312.60 <SUBJECT>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><HED>PART 812--INVESTIGATIONAL DEVICE EXEMPTIONS**

<AMDPAR>6. The authority citation for part 812 continues to read as follows:

<AUTH><HED>Authority: <P> 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360bbb-8b, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b-263n.

<AMDPAR>7. Revise § 812.2 (b)(1)(iii) to read as follows:

**<SECTION><SECTNO>§ 812.2<SUBJECT> 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.

\* \* \* \* \*

<SIG><DATED>Dated: November 7, 2018.

<NAME>Scott Gottlieb,

<TITLE>Commissioner of Food and Drugs.</SIG>

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