

Comment on FDA Proposed Rule: *Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Investigations*, 83 FR 57378 (proposed Nov. 15, 2018), FDA-2018-N-2727

Authors:¹ Kelly Todd and Daniel Kennedy

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Executive Summary

The FDA has proposed a Rule that would allow IRBs to waive or alter informed consent requirements for minimal risk research that would otherwise be subject to the informed consent requirements of 21 C.F.R. § 50. In order for an IRB to approve a request for waiver or alteration under the proposed Rule, it must find and document that four safeguards have been met. These four criteria track the 1991 iteration of the Common Rule. However, the Common Rule was revised in 2017 to add a fifth criterion that provides specific protections for research using identifiable private information or biospecimens.

This Comment addresses the FDA’s request for public comment as to whether the fifth criterion is necessary. This Comment will first discuss the revisions made to the Common Rule in 2017, and what those revisions say about the protections that are demanded when using modern research methodologies. Then, we will discuss what research qualifies as “human subjects” research. Finally, this Comment considers whether there are any types of FDA-regulated research that implicate the fifth criterion and might be considered minimal risk. Ultimately, we recommend that the FDA’s final Rule adopt the fifth criterion, and make further recommendations concerning what additional revisions may be necessary to clarify the Rule.

¹ The authors are graduate students in the Duke Science Regulation Lab, an interdisciplinary course offered through the Duke Law and Graduate Schools. Michael B. Waitzkin is the faculty member who runs the Science Regulation Lab, with the assistance of J.H. Pate Skene and Sarah Rispin-Sedlak. Misha Angrist, Senior Fellow in Duke Science and Society and Associate Professor of the Practice in the Social Science Research Institute, oversaw the preparation of this Comment.

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I. Introduction

A. Who We Are

The Duke Science Regulation Lab (“SciReg Lab”) is composed of graduate students from a variety of disciplines at Duke University, including science, law, ethics, and policy. The Science Regulation Lab was originally inspired by the traditional role of *amicus curiae*: to provide a court with unbiased information necessary to reach a binding decision. As an extension of that concept, we now provide government agencies with the scientific information necessary to undertake effective rulemaking.

Modern society requires our government to handle increasingly complex scientific issues when deciding cases or making policy. We, the Duke Science Regulation Lab, believe that the general public benefits from judgments that are based on sound scientific knowledge. To assist decision makers in understanding a scientific matter at hand, the students of the Science Regulation Lab combine their expertise to offer a non-partisan, accurate, and accessible explanatory brief or comment.

The members of the Duke Science Regulation Lab vary in their academic backgrounds. **Kelly Todd** is a 2019 JD candidate who is jointly pursuing a Master’s in Bioethics & Science Policy. **Daniel Kennedy** is a 2019 JD candidate.

B. Introduction to the Proposed Rule

On November 15th, 2018, the Food and Drug Administration (“FDA”) published a proposed rule entitled “Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Investigations” in the Federal Register.² The FDA proposed this Rule to amend its

² Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Investigations, 83 Fed. Reg. 57378 (proposed Nov. 15, 2018) (to be codified at 21 C.F.R. pts. 50, 312, & 812).

regulations to implement section 3024 of the 21st Century Cures Act,³ which granted the FDA the authority to waive or alter informed consent requirements for certain clinical research that poses no more than minimal risk to human subjects.⁴

If finalized, the proposed Rule would allow Institutional Review Boards (“IRBs”) that are responsible for the review, approval, and continuing review of FDA-regulated human subjects research to approve informed consent procedures that alter elements of the informed consent process, or waive the requirement to obtain informed consent, under certain conditions.⁵ The Rule would allow IRBs to make this determination for clinical testing that poses no more than “minimal risk” to the human subjects involved.⁶ According to the FDA’s definition, “minimal risk” means 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.”⁷

Section 3024 of the 21st Century Cures Act limits the FDA’s authority to permit altered or waived informed consent procedures for minimal risk research to situations in which “appropriate safeguards” exist “to protect the rights, safety, and welfare of the human subject.”⁸ To ensure that such appropriate safeguards are present, the FDA’s proposed Rule would require IRBs to find and document four criteria that are consistent with the “Federal Policy for the Protection of Human Subjects” (the “Common Rule”).⁹ The criteria include 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;

³ 21st Century Cures Act, Pub. L. No. 114-255, § 3024, 130 Stat. 1099 (2016).

⁴ *Id.*

⁵ 83 Fed. Reg. 57378, 57379.

⁶ *Id.*

⁷ 21 C.F.R. 50.3(k).

⁸ 21st Century Cures Act, Pub. L. No. 114-255, § 3024, 130 Stat. 1099 (2016).

⁹ Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003 (June 18, 1991).

- (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.¹⁰

The four criteria proposed by the FDA track the 1991 version of the Common Rule, which established standards for the protection of human subjects involved in federally funded research. The inclusion of these criteria brings the FDA into somewhat closer alignment with the Common Rule, as is mandated by section 3023 of the 21st Century Cures Act, which requires the Secretary “to the extent practicable and consistent with other statutory provisions, harmonize differences between the HHS Human Subject Regulations and the FDA Human Subject Regulations”¹¹

However, the Common Rule was revised in 2017 to include a fifth criterion: “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.”¹² The effective date for the revised Common Rule was January 21st, 2019.¹³ The FDA does not propose to include this fifth criterion. The agency did not provide an explanation for this decision, but seeks public comment on the issue.¹⁴ As such, the intent of this Comment is to provide insight into the purpose of the fifth criterion, the 2017 revisions to the Common Rule, and the implications of the FDA’s proposed Rule for industry and research participants.

¹⁰ 83 Fed. Reg. 57378, 57381.

¹¹ 21st Century Cures Act, at § 3023.

¹² Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7267 (Jan. 19, 2017).

¹³ Federal Policy for the Protection of Human Subjects: Six Month Delay of the General Compliance Date of Revisions While Allowing the Use of Three Burden-Reducing Provisions During the Delay Period, 83 Fed. Reg. 28497 (June 19, 2018).

¹⁴ 83 Fed. Reg. 57378, 57381.

II. Analysis of the Fifth Criterion

A. 2017 Revision to the Common Rule

The Common Rule was originally adopted in 1991 to codify the ethical principles identified in the Belmont Report.¹⁵ This report was the work product of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was established amid the backlash of the infamous Tuskegee syphilis study.¹⁶ The study recruited hundreds of rural African American men under the auspices of providing free medical care.¹⁷ However, unbeknownst to the research subjects, the purpose of the study was to chart the natural progression of syphilis.¹⁸ Participants who were diagnosed with syphilis were not alerted to their condition, or provided the medical treatment that, during the course of the study, had become the norm.¹⁹ In response to these gross injustices, the National Commission was tasked with identifying the basic ethical principles that should guide research involving human subjects.²⁰

The ethical principles identified by the Belmont Report and codified by the Common Rule include respect for persons, beneficence (including its corollary, nonmaleficence), and justice.²¹ The principle of respect for persons requires researchers to respect a research subject's autonomous decision-making, and is the principle most relevant to informed consent

¹⁵ OFFICE FOR HUMAN RESEARCH PROTS., *Federal Policy for the Protection of Human Subjects* (“Common Rule”), U.S. DEP’T HEALTH & HUM. SERVS. (Mar. 18, 2016), <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html> [<https://perma.cc/M78C-3QUP>].

¹⁶ Roger L. Bertholf, *Protecting Human Research Subjects*, 31 ANNALS CLINICAL & LABORATORY SCI. 119, 121 (2001).

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ *Id.* at 122.

²¹ *Id.*

procedures.²² The Common Rule therefore places requirements on researchers to explain the purposes of their research, risks and benefits of participation, what mechanisms are in place to ensure confidentiality, and other information that a reasonable person would want to have in order to make an informed decision.²³

Over the past few decades, advancements in modern biotechnology and data analysis have sparked concerns over what types of research should constitute “human subjects research” for which obtaining informed consent is required. Under the 1991 Common Rule, “human subjects” were defined as individuals about whom a researcher obtained “[d]ata through intervention or interaction with the individual,” or “[i]dentifiable private information.”²⁴ The original Common Rule also included exemptions from IRB oversight and informed consent requirements for research that involved collecting or studying “existing data, documents, records, pathological specimens, or diagnostic specimens” that were publicly available, or for which the researcher records the information “in such a manner that subjects cannot be identified.”²⁵ These definitions and exclusions proved to be a poor fit for the shift in human subjects research that occurred around the turn of the century: Data analytics, big data, and the digitization of health care information have created vast sources of mineable health information, while improved preservation and laboratory analysis practices have opened more doors for secondary uses of biological specimens, and genetic sequencing has allowed researchers (and clinicians) to extract large amounts of highly valuable, but highly personal, health information.

These shifts in research were accompanied by confusion as to what types of research qualified as “human subjects research” that must comply with the Common Rule’s requirements

²² *Id.*

²³ 45 C.F.R. § 46.116.

²⁴ Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003 (June 18, 1991).

²⁵ *Id.*

for IRB review and informed consent. In an editorial published alongside direct-to-consumer genetics company 23andMe’s first genome-wide association study in *PLoS Genetics* in 2010, editors of the journal suggested that the existing framework created an “unfortunate loophole” that excused investigators from obtaining informed consent in situations where the criteria for “human subjects research” might not be met, but informed consent would still be desirable.²⁶ The company had carried out the study on its customers without IRB oversight. When questioned by reviewers about the lack of informed consent, 23andMe employed an independent IRB that, relying on a 2008 guidance from the Office for Human Research Protections regarding research involving coded private information or biospecimens, validated 23andMe’s actions after-the-fact by declaring that the research was not “human subjects research” that required obtaining informed consent.²⁷ Invoking the plight of unwitting research subject Henrietta Lacks (from whom the famous HeLa cell line was derived), the *PLoS* editors urged sensitivity to the “ethical and moral concerns surrounding consent and research with human samples.”²⁸

In 2011, the Department of Health and Human Services (“HHS”) took the first concrete steps towards addressing these concerns by proposing the first major revisions to the Common Rule. In its Advanced Notice of Proposed Rulemaking (“ANPRM”) published on July 26th, 2011, HHS cited the rapid “growth and expansion of human subjects research” as the key instigator for the proposed changes.²⁹ According to the ANPRM, human subjects research was

²⁶ Greg Gibson & Gregory P. Copenhaver, Editorial, *Consent and Internet-Enabled Human Genomics*, 6 PLOS GENETICS (June 2010), <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.604.2223&rep=rep1&type=pdf>.

²⁷ *Id.*

²⁸ *Id.*

²⁹ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44513 (proposed July 26, 2011).

not just growing in volume,³⁰ but expanding to include new participants,³¹ new methodologies,³² and new technologies.³³ The ANPRM identified seven areas of concern that its revisions aimed to address, including criticisms that IRB review processes were not adequately calibrated to the risks of the research, that informed consent requirements were lacking in quality, and, significantly, that the “increasing use of genetic information, existing (i.e., stored) biospecimens, medical records, and administrative claims data in research has changed the nature of the risks and benefits of research participation.”³⁴ These growing types of research involve non-negligible risks that are “not physical but informational (e.g., resulting from the unauthorized release of information about subjects).”³⁵

Four years after publication of the ANPRM, HHS released a revised Notice of Proposed Rulemaking (“NPRM”).³⁶ After further revision, the final Rule was published in the Federal Register on January 19th, 2017, President Obama’s last day in office.³⁷ The ANPRM, NPRM, and final Rule all reflect serious considerations on the part of HHS as to how best to facilitate new research while protecting participants from the informational risks associated with modern research practices.

³⁰ *See id.* (“It is estimated that total spending on health-related research and development by the drug industry and the Federal government has tripled since 1990.”).

³¹ *See id.* (“Recruitment firms, bioinformatics specialists, clinical trial coordinating centers, protocol developers, data analysts, contract research organizations (CROs), data and safety monitoring committees, community-based organizations, and other entities have joined investigators and sponsors as part of the clinical research enterprise.”).

³² *See id.* (“The application of technologies such as functional magnetic resonance imaging in neuroscience has led to substantial advances in the understanding of human physiology, cognition, and behavior.”).

³³ *See id.* (“The advent of sophisticated computer software programs, the Internet, and mobile technology have created new areas of research activity, particularly within the social and behavioral sciences, exponentially increasing the amount of information available to researchers, while providing the means to access and analyze that information.”).

³⁴ *Id.* at 44513–14.

³⁵ *Id.* at 44514.

³⁶ Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53933 (proposed Sept. 8, 2015).

³⁷ Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149 (proposed Jan. 19, 2017).

One of the major concerns reflected in the revisions to the Common Rule is the issue of identifiability, and the risks it poses to participants whose information or specimens are used in research. In its 2011 ANPRM, HHS noted that many consider the line between what is “identifiable” versus “de-identified” data to be “fluid,” as rapidly evolving technology and expanding volumes of data increase the likelihood that what is currently considered de-identified data may soon become identifiable.³⁸ As such, HHS devoted significant portions of its ANPRM, NPRM, and final Rule to discussing proposed revisions concerning researchers’ use of identifiable information and biospecimens, information risks, and how those risks should be addressed and minimized. One of the most controversial revisions was proposed in the 2011 ANPRM, in which HHS considered expanding the definition of the term “human subjects” to encompass all biospecimens, regardless of identifiability.³⁹ While the provision was ultimately deemed too restrictive and thus not included in the final Rule, the final Rule accounts for the informational risks of the changing research landscape in a number of ways.

The 2017 Rule clarifies how to protect individuals in our modern research landscape by defining the types of identifiable information and biospecimens covered by the Rule, how often the standards for identifiability must be reviewed, when certain research utilizing identifiable information and biospecimens is exempt from the Common Rule’s consent requirements, and how IRBs should protect the privacy of subjects and maintain the confidentiality of their data. Importantly, the revised Rule also added new, additional protections tailored to research using private information or biospecimens to the human subject protection requirements that most research must comply with. For example, the revised Common Rule requires additional

³⁸ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44524 (proposed July 26, 2011).

³⁹ *Id.* at 44525.

disclosures to be made during the informed consent process if an individual’s identifiable private information or biospecimens are being used. The informed consent must state that the data will either not be used for future research, or that if it used for future research that it will be stripped of identifiers.⁴⁰ The revised Rule also suggests that the informed consent process notify participants as to whether and how their biospecimens will be used for commercial profit⁴¹ and/or be subject to genetic sequencing.⁴²

While these provisions generally increase human subject protections for research using private information and biospecimens, other revisions had different goals. When the Common Rule was revised in 2017, one of the guiding themes of the revisions was to assure that the regulatory framework facilitates valuable research by reducing undue burdens and delays.⁴³ The revised Rule therefore relaxed some requirements for specific types of research that has a certain risk profile. For example, one of the larger changes to the revised Common Rule established a tiered consent framework that permits researchers to procure broad consent for the “storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens,” as opposed to study-specific consent. While procuring broad consent exempts researchers from obtaining additional consent from subjects for future studies, the final Rule’s broad consent procedure establishes additional, forward-looking protections for research subjects, such as requiring information regarding the types of studies their information or specimens may be used for, and the period of time that their information or specimens may be stored and accessed, to be disclosed to the subject.

⁴⁰ Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7266 (proposed Jan. 19, 2017).

⁴¹ 45 C.F.R. 46.116(c)(7).

⁴² *Id.* at 46. 116(c)(9).

⁴³ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44512 (proposed July 26, 2011).

The final Rule illustrates the difficult balance that must be struck between respecting human subjects’ autonomy and protecting against the informational risks associated with modern research practices, and the scientific value presented by comprehensive analysis of health information and specimens. Research using private information or biospecimens does not present the kind of physical risks that are of the highest concern for human subject protections.⁴⁴ This allows for some leniency to facilitate efficient innovation. However, this research does present a new type of informational risk that can have significant implications for subjects. The 2017 revisions to the Common Rule suggest that traditional protections designed with physical risks and direct research methodologies in mind fail to adequately address this new type of risk, and further, tailored protections are warranted.

As a whole, the revised Common Rule reflects the difficult balance that is to be struck between the informational risks that modern research poses to research subjects, and the need to facilitate this research in order foster scientific and technological advancement. As the FDA works to bring itself more into alignment with the Common Rule, it too must consider how to achieve this balance.

B. Human Subjects Protections Under the FDA’s Informed Consent Regulations and the Revised Common Rule

While the FDA mirrors the Common Rule in a number of ways, a few important differences exist that may shift the balance of risks and benefits should the FDA finalize this proposed rule. First, while both the Common Rule and the FDA provide protections for human subjects research, they employ different definitions of the term “human subject.” The revised Common Rule defines a human subject as a “living individual about whom an investigator

⁴⁴ Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44513 (proposed July 26, 2011).

(whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.”⁴⁵ The Rule goes on to define the types of “private information” that is afforded protection under the second prong of its definition of “human subject” as “information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.*, a medical record).”⁴⁶

This provision saw some of the most significant changes in the 2017 revision of the Common Rule. Not only were biospecimens explicitly added to the definition of “human subject,” but identifiability became a key component in the determination of what is or is not human subjects research. The revised Rule added definitions for the terms “identifiable private information” and “identifiable biospecimen,” describing them as information or specimens “for which the identity of the subject is or may readily be ascertained by the investigator or associated with the [information/biospecimen].”⁴⁷ Recognizing the ambiguity of this definition and the reality that rapidly developing technologies may soon be capable of re-identifying data that is considered de-identified by today’s standards, the Common Rule places additional responsibilities on enacting agencies. The revised Rule requires those implementing the Rule to consult with experts to reexamine the meaning of “identifiable” information and biospecimens, and what technologies or techniques are considered to generate such information and

⁴⁵ 45 C.F.R. 46.102(e).

⁴⁶ *Id.*

⁴⁷ *Id.*

biospecimens.⁴⁸ The Rule recognizes the importance of keeping abreast of what is needed to protect subjects’ from identification by requiring agencies to conduct these examinations within one year of implementation, and at least every four years after that.⁴⁹

The FDA’s definition of “human subject” differs significantly. The FDA defines a “human subject” protected by its regulations as “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.”⁵⁰ While the requirement that subjects be either the recipient of an FDA-regulated test article or a control logically narrows the scope of the definition to match the FDA’s mission and statutory authority, the definition provides less guidance on when a subject qualifies as a participant in research. The FDA’s regulations at 21 C.F.R. § 50 are relatively silent as to what types of investigator-subject exchanges make one a participant, whereas the Common Rule specifically defines the interactions, interventions, information, and specimens that establish an individual as a research subject. While direct interactions and interventions between investigators and individuals seem to easily fall within the FDA’s definition, it is less clear whether research involving personal information or biospecimens is similarly protected. If such research does fall within the FDA’s definition of “human subject,” then it is subject to the FDA’s informed consent requirements, and those researchers might seek waivers or alterations in their informed consent procedures under the FDA’s proposed Rule.

With regard to whether research using biospecimens is “human subject” research, the FDA provided some insight in its 2006 guidance entitled “Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ 21 C.F.R. 50.3(g).

Identifiable.”⁵¹ The guidance refers to 21 C.F.R § 812, which exempts certain investigational devices from a number of FDA requirements. As is defined in that section, a “subject” is “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.”⁵² The definition is not limited to identifiable specimens. In its 2006 guidance, the FDA apparently extends, at least to investigational *in vitro* diagnostic devices seeking exemption, the definition that subjects deserving of the consent requirements enumerated in 21 C.F.R § 50 include individuals on whose identifiable or non-identifiable specimens an investigational device is used.⁵³ Otherwise, an explicit waiver of the informed consent requirements would be unnecessary. The FDA’s definition of “human subject” at 21 C.F.R § 50.3 therefore seems to inherently accommodate notions of participation in research that extend beyond direct interaction or intervention. The FDA’s current definition therefore potentially encompasses less direct methods of human research, such as research utilizing both identifiable and non-identifiable biospecimens, and/or private information.

C. Minimal Risk Research and Industry

As previously mentioned, both the FDA and the Common Rule share the same definition of “minimal risk,” that is, research in which “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily

⁵¹ *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*, FOOD & DRUG ADMIN. (Apr. 25, 2006), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf> [hereinafter *Guidance on Informed Consent*].

⁵² 21 C.F.R § 812.3(p).

⁵³ See *Guidance on Informed Consent* (“Under FDA’s current regulations governing the conduct of IVD device studies, the definition of human subject includes individuals on whose specimens an investigational device is used. Because these regulations require informed consent for FDA-regulated human subject research . . . informed consent is required before specimens can be used in FDA-regulated research.”).

encountered in daily life or during the performance of routine physical or psychological examinations or tests.”⁵⁴ However, the FDA’s proposed Rule provides no further guidance or examples illuminating the types of FDA-regulated research that might qualify as minimal risk. This may be particularly problematic as IRBs “report challenges in assessing the level of risk presented by some studies in order to make the critical minimal risk determination.”⁵⁵ A significant body of literature indicates that there are high levels of variability and inconsistency among IRB methodologies and review, including for minimal risk research.⁵⁶ Research indicates that IRBs are particularly challenged by the types of modern genetic and biospecimens research that prompted many of the most significant changes finalized in the 2017 Common Rule. In one study, IRBs evaluating the risk of the same genetic epidemiologic study returned responses ranging from minimal to high, with about ¼ of the IRBs determining that the study met the minimal risk requirements to qualify for expedited review.⁵⁷ Another study returned very heterogeneous results for IRB classification of research using identified biospecimens as “no greater than minimal risk” or “greater than minimal risk.”⁵⁸

While the FDA’s proposed Rule provides no guidance for making the critical “minimal risk” determination, other FDA and HHS regulations and guidance may provide some insight as to what types of research may qualify. Both the FDA and the Common Rule have long permitted expedited IRB review procedures for certain research that poses no more than minimal risk, and falls into one of the enumerated categories of research. The FDA’s list of categories eligible for

⁵⁴ 21 C.F.R § 50.3(k), 45 C.F.R. § 46.102(j).

⁵⁵ Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,172 (Jan. 19, 2017).

⁵⁶ Jon Mark Hirshon et al., *Variability in Institutional Review Board Assessment of Minimal-Risk Research*, 9 ACAD. EMERGENCY MED. 1417, 1417 (2002).

⁵⁷ Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 J. AM. MED. ASS’N 360, 360 (2003).

⁵⁸ Aaron J. Goldenberg et al., *IRB Practices and Policies Regarding the Secondary Research Use of Biospecimens*, 16 BMC MED. ETHICS no. 32, 3 (2015).

expedited review under 21 C.F.R. § 56.110 was published via notice in the Federal Register in 1998.⁵⁹ The list includes, among others, clinical studies of drugs or devices only if it is research for which an investigational new drug application or investigational device exemption is not required, noninvasive collection of biospecimens or data for research purposes, and research on group characteristics or that employs certain methodologies, such as surveys.⁶⁰ The FDA’s list shares significant overlap with the categories of research HHS deems eligible for expedited review under 45 C.F.R. § 46.110. However, HHS’s list includes additional categories, such as minimally invasive collection of biospecimens for research purposes, activities at data coordinating centers or biospecimen repositories, and secondary research uses for identifiable private information and identifiable biospecimens in certain situations.⁶¹

While the FDA’s and HHS’s enumerated lists of categories eligible for expedited IRB review provide some benchmarks for what types of research are “minimal risk,” their applications are limited. Neither the Common Rule nor the FDA’s proposed Rule similarly limit the types of research eligible for waivers or alterations in informed consent to certain categories of research. In the expedited IRB review context, these categories both limit, and are limited by, what types of research qualify as minimal risk. Research may fall within one of these categories, but may not be deemed “minimal risk” by an IRB. There may also be research that could properly be deemed “minimal risk,” but that does not fall within one of the enumerated categories. Therefore, while the categories of research eligible for expedited review provide

⁵⁹ Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, 63 Fed. Reg. 60,353 (Nov. 9, 1998).

⁶⁰ *Id.*

⁶¹ Attachment A, Recommendations on the Expedited Review List, DEP’T HEALTH & HUM. SERVS., <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-december-12-2017/index.html>.

some guidelines as to what types of research may make use of the FDA’s proposed pathway, the boundaries of what will qualify as minimal risk research are unclear.

Using these categories as rough guidelines for the types of studies that have a colorable argument for being “minimal risk” suggests that there are a number of areas of FDA-regulated research where waivers or alterations in informed consent procedures might be sought under the proposed Rule. One such example may be cluster randomized studies gathering real world evidence.⁶² Relevant to the issue of the excluded fifth criterion is whether research using identifiable private information or identifiable biospecimens might qualify for this pathway. We believe this is likely, and that such instances would be consistent with the general notions of minimal risk research discussed elsewhere in FDA regulations and the Common Rule. HHS’s list of research categories that are eligible for expedited review specifically includes certain types of research using identifiable private information and biospecimens, so researchers seeking a waiver or alteration in informed consent for such research under the FDA’s proposed Rule would be within their rights to seek such waivers/alterations.

What types of FDA-regulated research using biospecimens or private information might industry utilize this pathway for? With regard to biospecimens, and was previously discussed, the FDA’s definition of “human subject” must be broad enough to encompass some research involving biospecimens. At a minimum, research using identifiable biospecimens likely falls within the FDA’s definition of “human subject” and is therefore subject to the informed consent requirements in 21 C.F.R. § 50. As many researchers have confirmed, “biospecimens are important for drug and diagnostics co-development,”⁶³ and the FDA will likely see more of this

⁶² See Attachment B, Recommendations on Regulatory Issues in Cluster Randomized Studies, DEP’T HEALTH & HUM. SERVS., <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html>.

⁶³ Jim Vaught, *Developments in Biospecimen Research*, 114 BRIT. MED. BULL. 29, 35 (2015).

type of research falling under the scope of its authority and making use of the flexibilities built into 21 C.F.R. § 50. An *in vitro* diagnostic device study that uses identifiable biopecimens collected through noninvasive means is one type of research that would seem to fall under the FDA’s informed consent requirements, and could possibly qualify as minimal risk research for which a waiver of or alteration in consent would be approved.

With regard to research using identifiable private information, it is less clear whether such research would fall under the FDA’s definition of “human subject,” and therefore be subject to the informed consent requirements in 21 C.F.R. § 50. However, the FDA will likely see such research coming increasingly under its purview in the future. The 21st Century Cures Act authorizes the FDA to consider evidence beyond clinical trials to support its regulatory decision-making, including “real world evidence.”⁶⁴ According to the FDA, real world data may come from sources such as “electronic health records.”⁶⁵ In a 2018 guidance on the “Use of Electronic Health Record Data in Clinical Investigations,” the FDA outlined how investigators conducting such research can comply with the requirements of 21 C.F.R. § 50 “[w]hen informed consent is required.”⁶⁶ This suggests that some research involving identifiable private information is subject to the informed consent requirements in 21 C.F.R. § 50. Researchers investigating electronic health records to develop real world evidence that will be included in an application to the FDA could likely make a compelling case that such research is of no more than minimal risk, and therefore that the informed consent requirements should be waived or altered under the FDA’s proposed Rule. This would have a significant impact on industry, as electronic health records and

⁶⁴ 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1096 (2016).

⁶⁵ *Real World Evidence*, FOOD & DRUG ADMIN. (Feb. 6, 2019), <https://www.fda.gov/ScienceResearch/SpecialTopics/RealWorldEvidence/default.htm>.

⁶⁶ Use of Electronic Health Record Data in Clinical Investigations, FOOD & DRUG ADMIN. (July 2018), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf>.

other real world evidence have become increasingly valuable for drug development in the era of big data.⁶⁷ Among other uses, research using electronic health records can aid drug discovery by “finding novel relationships between diseases, re-evaluating drug usage, and discovering phenotype–genotype associations.”⁶⁸

According to the analyses above, it seems both possible and likely that some FDA-regulated research using identifiable private information and biospecimens is subject to the informed consent requirements of 21 C.F.R. § 50, and could be considered minimal risk research that might make use of the FDA’s proposed Rule.

III. Our Recommendations

A. The Final Rule Should Incorporate the Excluded Criterion

The final Rule should incorporate the excluded fifth criterion, that an IRB must find, “[i]f the research involves using identifiable private information or identifiable biospecimens, [that] the research could not practicably be carried out without using such information or biospecimens in an identifiable format.” As our analyses above indicate, some research using identifiable private information and identifiable biospecimens is subject to the informed consent requirements of 21 C.F.R. § 50. Industry has been increasingly relying on these methodologies for the development of drugs, diagnostics, and devices in recent years, so the real world implications of the fifth criterion are not hypothetical. Some of this research likely qualifies as minimal risk research, and may therefore make use of the informed consent waiver and alteration provision proposed by the FDA. Should the fifth criterion be excluded from the final Rule, it will

⁶⁷ Lixia Yao et al., *Electronic Health Records: Implications for Drug Discovery*, 16 DRUG DISCOVERY TODAY 594, 594 (2011).

⁶⁸ *Id.*

deny a safeguard that is directly on point for an important category of research that has recently been at the forefront of human subject protection discussions.

The criteria that an IRB must find and document before approving of an alteration or waiver of informed consent essentially operate as a balancing tool. They balance potential risks (*e.g.*, that a waiver might affect the rights of its participants) against the benefits of easier and more efficient research. When one of the criteria are not met, the risks outweigh the benefits and the waiver or alteration cannot be approved. As was previously discussed, the risks presented by research using identifiable private information and biospecimens are informational in nature. The fifth criterion limits these risks by requiring that the research is carried out in a de-identified format where possible. Without the fifth criterion, IRBs will still be faced with applications to waive or alter informed consent for studies involving identifiable private information or biospecimens. However, in those cases the identifiability of the data will not be given the protections that the informational risks it presents demands because identifiability is not a factor of concern in the FDA's proposed Rule. We argue, and the 2017 revisions to the Common Rule support, that the risks presented by using identifiable data in research are not insignificant. Requiring de-identification in situations in which it is practicably achievable is a necessary check on the informational risks the research presents.

One counterargument to including the fifth criterion is that it is unnecessary because the IRB must already determine whether the identifiability of the information or specimens present only minimal risk. If the identifiability of the information presents more than a minimal risk, the study will be ineligible for a waiver or alteration anyway. Therefore, by demanding de-identification, the fifth criterion requires research using private information or biospecimens to meet an even higher standard of *de minimis* or nonexistent risk to qualify for a waiver or

alteration. Therefore, it is unnecessary. For a number of reasons, we disagree. First, minimal risk is only one factor in the IRB’s analysis. For example, a study that presents no more than minimal risk will nonetheless be denied a waiver or alteration if it is practicable to obtain formal informed consent. Only the first proposed criteria relates to risk—the three other proposed criteria are additional safeguards outside the realm of risk that further define situations in which a waiver or alteration of informed consent is appropriate. While requiring de-identification does decrease the risk of the study, it also serves other functions. For example, it protects individuals from becoming unwitting, or unwilling, research subjects. When investigators do not interact or intervene directly with individuals, they may have little or no expectation that their information or specimens may be used in research at all. According to a recent study of 23andMe users, three in four are uncomfortable with the idea of commercial pharmaceutical companies having access to their leftover specimens for research purposes.⁶⁹ Requiring de-identification where possible maintains consent as a barrier protecting individuals from becoming identifiable subjects in research without permission.

B. Additional Revisions to FDA Informed Consent Regulations Are Needed

Should the FDA include the fifth criterion, additional revisions to FDA regulations are likely needed to add clarity and consistency to the regulatory scheme. First, the FDA should revise its definition of “human subject” at 21 C.F.R. § 50.3(g) to clarify the applicability of § 50 to private information and biospecimens. The current definition presents both normative and substantive inconsistencies with how private information and biospecimens are treated within § 50 and elsewhere in title 21.

⁶⁹ Kayte Spector-Bagdady et al., *Encouraging Participation and Transparency in Biobank Research*, 37 HEALTH AFF. 1313 (2018).

Inclusion of the fifth criterion will also require IRBs to make determinations regarding identifiability, including whether private information or biospecimens are identifiable, and therefore invoke the fifth criterion, and what must be required for identifiable information and specimens to be properly and sufficiently de-identified. As was previously discussed, identifiability is more fluid than the term implies, and technology is rapidly changing how data can be identified. Therefore, we recommend that the FDA adopt a provision similar to § 46.102(d)(7) of the Common Rule, which would require that the FDA periodically reevaluate the meaning of “identifiable,” and what technologies or techniques generate identifiable information or specimens. Such a provision would provide much needed guidance for IRBs when addressing the complex question of identifiability.

While researchers and human subjects whose identifiable private information or biospecimens are used in FDA-regulated research may benefit from the FDA adopting other provisions of the revised Common Rule, we limit our recommendation to the two provisions mentioned as they have the greatest bearing on the fifth criterion of the proposed Rule.

IV. Conclusion

Though the FDA’s proposed Rule excludes criteria mentioning safeguards for identifiable private information and identifiable biospecimens, the reality of the modern research climate is that these types of research are likely subject to the FDA’s informed consent requirements, and are likely to prompt researchers to request alterations or waivers of informed consent under the proposed provision. Research using identifiable information and specimens present informational risks that both the public, and the revised Common Rule, take seriously. The fifth criterion protects the autonomy of those whose information or specimens are used in research by generally making consent a requirement, even for minimal risk studies, when riskier, identifiable data is

used. Requiring IRBs to assure that information or specimens are de-identified whenever possible in order for researchers to waive or alter informed consent procedures is therefore an appropriate and necessary safeguard.