COMMENT

COMMON COURTESY: HOW THE NEW COMMON RULE STRENGTHENS HUMAN SUBJECT PROTECTION*

ABSTRACT

Medical science and research depend on human subject testing. In the United States, the Federal Policy for the Protection of Human Subjects, colloquially known as the "Common Rule," is the regulation ensuring the protection and dignity of all human subjects. Whether the participants are answering questionnaires or testing prescriptions, the Common Rule describes the ethical requirements of testing on human subjects. Initially promulgated in 1991, the Common Rule has remained mostly unchanged, despite the vast changes in human subject research. As technology changes, the current regulations are failing to provide adequate protection to research participants. In response, the Department of Health and Human Services published an Advanced Notice of Public Rule Making in the Federal Register in 2011. Four years later, on September 8, 2015, HHS published a Notice of Proposed Rule Making in the Federal Register. On January 19, 2017, the final rule for the Federal Policy for the Protection of Human Subjects was announced.

This Comment analyzes the relationship between the NPRM and the Final Rule regarding three specific protections of the Common Rule regulations proposed in the NPRM: (1) the additions to the informed consent documents; (2) the evolving role

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of the Internal Review Board's obligations and procedures; and (3) the treatment of secondary biospecimens. Further, this Comment addresses the history of human testing, the current Common Rule, the proposed changes, and the implications of the Final Rule. In doing so, this Comment analyzes submitted public comments to the Notice of Proposed Rule Making and how the Final Rule incorporates, or fails to incorporate, these provisions. The Final Rule shows that despite the failure to incorporate every aspect of the proposed rule, the changes to the Common Rule will promote human subject dignity and autonomy without jeopardizing crucial, and much-needed, research.

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I. INTRODUCTION

> Many scientists are afraid of involving people in research as a partnership as if they have a fear of something being taken or stolen from them. But can't we say the same to them?[1]

Medical science and research depends on human subject testing.[2] Testing on human participants is imperative to the discovery of life-changing medicine, tests, and treatments.[3] Human testing involves great responsibility that has historically left vulnerable groups in dangerous or compromising situations.[4] To combat these challenges, bioethicists have advocated for continually evolving protections in the field of human subject research. While the road to regulation has been tumultuous, and sometimes tragic, the research community has made great strides in protecting the individuals involved in research studies.[5]

In the United States, the Federal Policy for the Protection of Human Subjects,[6] colloquially known as the "Common Rule," is the current regulation to ensure the protection of all human subjects.[7] Initially promulgated in 1991, the Common Rule has remained mostly unchanged for the past quarter century, despite the vast changes in human subject research.[8] As human subject research continues, the current regulations are failing to provide adequate protection to research participants.[9] In response to this,

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1. Lacks Family, Comment Letter on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 8, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-2138 [https://perma.cc/9ARW-ASPQ].

2. *See generally* Harold T. Shapiro, Ethical Considerations in Research on Human Subjects: A Time For Change… Again, Raymond Waggoner Lecture at 1–4, 6 (Dec. 5, 2001), https://www.princeton.edu/~hts/PDFs/Considerations.pdf [https://perma.cc/K3RP-229F] (discussing the importance of biomedical research and human subject testing).

3. *See infra* Part II.B (discussing the ethical controversies affecting low-income and minority groups throughout U.S. history).

4. *See infra* Part II.B; *see also infra* Part II.C (outlining the advances in human subject regulations resulting in more stringent protections for research participants).

5. *See infra* notes 89–94 and accompanying text (outlining the road to the current regulations of human research).

6. 45 C.F.R. § 46.101 (2005).

7. *Federal Policy for the Protection of Human Subjects ('Common Rule')*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html [https://perma.cc/8JJP-PKVU].

8. The original Common Rule was promulgated in 1991 and was amended in 2005. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7149 (Jan. 19, 2017). The Common Rule has not been amended since 2005. *Id.*

9. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,512 (July 26, 2011) ("[The regulations] have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral

Health and Human Services ("HHS") published an Advanced Notice of Public Rule Making (the "ANPRM") in the Federal Register in 2011.[10] Four years later, on September 8, 2015, HHS published a Notice of Proposed Rule Making (the "NPRM") in the Federal Register.[11] A little over a year later, on January 19, 2017, HHS, in conjunction with fifteen other federal departments and agencies, promulgated the final rule (the "Final Rule") for the Federal Policy for the protection of Human Subjects.[12]

The Common Rule extends far beyond medical research. The Common Rule governs all research conducted on humans.[13] Whether the participants are answering questionnaires or testing prescriptions, the Common Rule describes the ethical requirements of testing on human subjects.[14] This expansive rule covers fifteen federal agencies, from the Department of Health and Human Services to the Department of Commerce.[15] The Final Rule implicates numerous areas of law, such as health law, statutory interpretation, constitutional law, and intellectual property law. The breadth of the Common Rule's coverage highlights the importance of adequate human subject protection and why updating the Common Rule was necessary to ensure the integrity of research.

While the reach of the proposed changes and Final Rule are broad, this Comment will analyze the relationship between the NPRM and the Final Rule regarding three specific protections of the Common Rule regulations proposed in the NPRM: (1) the additions to the informed consent documents; (2) the evolving role of the Internal Review Board's (the "IRB") obligations and procedures; and (3) the treatment of secondary biospecimens. While these provisions were not adopted verbatim in their entirety in the Final rule, they signify three areas of conflicting bioethical considerations for HHS.[16] Further, this Comment will address the

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sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics.").

10. *Id.*; *see also infra* notes 146–60 and accompanying text (discussing the ANPRM proposed in 2011).

11. *See* Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,933 (Sept. 8, 2015) ("This NPRM seeks comment on proposals to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators.").

12. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7149.

13. *Id.* ("Research with human subjects has grown in scale and become more diverse.").

14. 45 C.F.R. § 46.101(a) (2005).

15. *Id.*; *Federal Policy for the Protection of Human Subjects*, *supra* note 7.

16. *See generally* Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7149 (failing to adopt the recommendation by the NPRM to require nonidentified

history of human testing, the current Common Rule, the proposed changes to the Common Rule, and the implications of the Final Rule. In Part II, the history of human subject research, and the protections afforded to them, will be examined by studying history, past statutory requirements, ethical violations, and case law. Part III dissects the Common Rule as originally passed in 1991 and gives a brief overview of the current statutory provisions. This section addresses the two primary protections guaranteed by the Common Rule: informed consent and the IRB. Part IV discusses the need for change within the regulatory framework of the Common Rule and outlines the proposed changes to the Common Rule. Part V reviews the comments submitted by interested persons for the NPRM and analyzes how these ideas were or were not implemented into the Final Rule. Finally, the conclusion will project the long-term impacts of the Final Rule, focusing on whether these changes will prioritize personal autonomy of human subjects and strengthen the overall integrity of human subject research.

II. THE HISTORY OF PROTECTING HUMAN SPECIMENS

Neither the Final Rule nor the NPRM is the first attempt to regulate human subject testing. Medical science is not a novel subject; in fact, it can be traced back to the biblical days and beyond.[17] Fast forward to today, science and technology are developing at a faster pace than ever. With each new breakthrough, researchers want to test the efficacy of their results on humans. This section discusses the history of medical testing on humans, beginning with the Ancient Greek approach to medicinal testing through some of the ethical dilemmas that researchers face today. An analysis of the history of human testing reveals that the struggles the Final Rule seeks to address, as proposed in the NPRM, are not novel issues.[18]

A. The Beginning of Human Subject Testing

Regulation of human subjects testing did not begin in the United States. The Ancient Greeks were first to express ethical

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biospecimens be subject to the Common Rule, but incorporating changes to IRBS and broad informed consent).

17. *See, e.g.*, *Jeremiah* 30:13 (King James) ("There is none to plead thy cause, that thou mayest be bound up: thou hast *no healing medicines*.") (emphasis added); 2 *Chronicles* 16:12 (King James) ("[Y]et in his disease he sought not to the LORD, but to the physicians.").

18. *See infra* Part II.B (describing issues and ethical violations that have led to the current statutory framework of the Common Rule).

convictions for human subjects and patients. The Hippocratic Oath was one of the first publications to address the doctor's ethical duties to a patient.[19] This oath, still administered to medical students today, also provides that the doctor will do no harm to his or her patient.[20] This oath in no way addresses informed consent or the rights of a patient; rather, it simply addresses what a doctor will provide to the patient.[21] The Hippocratic Oath is one of the earliest sources evidencing the idea of respect for patient autonomy. The oath remains relevant today, especially in a world of big data.[22] While there are many changes in how research is conducted, the ideas behind the Hippocratic Oath remain the same: every patient is entitled to respect and privacy.[23] The Hippocratic Oath provided a critical precedent for the first major human subject regulation in the United States, the Belmont Report.[24]

Modern bioethics arrived as a product of one of the most tragic events in human history.[25] During the course of the Second World War, Nazi doctors conducted horrific and cruel experiments on prisoners to gather scientific data.[26] These experiments involved unethical methods such as injecting prisoners with typhus, syphilis, and tuberculosis.[27] Other atrocities included strapping children down to make incisions and scrape their bones without the use of pain medication or anesthesia.[28]

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19. HIPPOCRATIC WRITINGS 67 (G.E.R. Lloyd ed., J. Chadwick & W.N. Mann trans., Penguin Classics 1983) (1950); Joel Sparks, *Timeline of Laws Related to the Protection of Human Subjects*, NAT'L INSTS. OF HEALTH: OFFICE OF HISTORY (June 2002), https://history.nih.gov/about/timelines_laws_human.html [https://perma.cc/6H8C-35HE].

20. HIPPOCRATIC WRITINGS, *supra* note 19, at 67.

21. *Id.* Adherence to the oath has never been a formal requirement to practice medicine. Erich H. Loewy, *Oaths for Physicians—Necessary Protection or Elaborate Hoax?*, MEDSCAPE GEN. MED. (Jan. 10, 2007), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1925028/.

22. Hagop Kantarjian & David P. Steensma, *Relevance of the Hippocratic Oath in the 21st Century*, ASCO POST (Oct. 15, 2014), http://www.ascopost.com/issues/october-15,-2014/relevance-of-the-hippocratic-oath-in-the-21st-century.aspx [https://perma.cc/DZP4-LGWW].

23. *Id.*

24. *See infra* notes 80–81 and accompanying text (outlining the three basic ethical principles of the Belmont Report).

25. Sparks, *supra* note 19.

26. Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERKELEY J. INT'L L. 513, 521–22 (2002).

27. *Id.*; WHEN MEDICINE WENT MAD: BIOETHICS AND THE HOLOCAUST 10 (Arthur L. Caplan ed., 1992).

28. WHEN MEDICINE WENT MAD, *supra* note 27, at 12.

These ghastly experiments led to a series of trials in 1946–1947 referred to as the Nuremberg Trials.[29] At the time of the Nuremberg Trials, human research guidelines were so poorly recorded that defense attorneys argued that these horrible acts complied with acceptable practices of Western Medicine.[30] The outcomes of these trials resulted in the creation of the Nuremberg Code.[31] The Nuremberg Code begins with the assertion that "the voluntary consent of the human subject is absolutely essential" and that all of medical ethics are built upon informed consent.[32] The Nuremberg Code also provides that the research must be scientifically necessary, conducted by qualified individuals, and that the benefit to science must be weighed against the amount of suffering and discomfort of the individual participants.[33] Despite the lack of adequate protection, the Nuremberg Code began the discussion of the importance of protecting human subjects in research. Finally, it acknowledged the unappealing idea that without proper regulation, terrible results can come from research.[34] While the Nuremberg Code was written in the late 1940s, ethical violations would continue in the United States for many more years. The following sections discuss the tragic road that led to the United States codifying protections for human subjects.

B. Case Law and Ethical Controversies in the United States

In addition to the tragedies that gave rise to the Nuremberg Code,[35] American case law has demonstrated the increasing need for regulation of human subject testing.[36] New York was the first

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29. NATIONAL ARCHIVES AND RECORDS SERVICE, RECORDS OF THE UNITED STATES NUREMBERG WAR CRIMES TRIALS: *UNITES STATES OF AMERICA V. KARL BRANDT ET AL.* (CASE I) NOVEMBER 21,1946–AUGUST 20, 1947, at 1, 3 (1974).

30. 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, at 72 (1949). Karl Brandt was the personal physician of Adolf Hitler and was associated with experiments conducted on prisoners involving high altitude, malaria, freezing mustard gas, sulphanilamide, jaundice, incendiary bombs, and sterilization. RECORDS OF THE UNITED STATES NUREMBERG WAR CRIMES TRIALS, *supra* note 29, at 3–4.

31. Meier, *supra* note 26, at 521.

32. *Id.* at 523–24.

33. 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS, *supra* note 30, at 181–82.

34. *See supra* notes 27–28 and accompanying text (describing the horrific Nuremberg experiments).

35. *See infra* notes 49–69 and accompanying text (discussing the Tuskegee Syphilis Study, Henrietta Lacks, and the Jesse Gelsinger case).

36. Wash. Univ. v. Catalona, 490 F.3d 667, 673–74 (8th Cir. 2007) (determining the ownership rights of biological material, such as blood and tissue sample removed during surgery); Havasupai Tribe v. Ariz. Bd. of Regents, 204 P.3d 1063, 1067 (Ariz. Ct. App. 2008)

state to address the rights of patients and informed consent over one hundred years ago in *Schloendorff v. Society of New York Hospital*.[37] Prior to any federal informed consent regulation, *Schloendorff* addressed whether a hospital could legally remove a tumor without the informed consent of the patient.[38] The facts of the case are as follows: the patient instructed the physicians not to perform an operation on a recently discovered lump in her stomach.[39] The following day, while the patient was under anesthesia, the doctor disregarded the patient's wishes and operated to remove the tumor.[40] The patient maintained that this was done without her consent or knowledge.[41] At trial, the court held that the operation without the consent of the patient was a trespass upon the woman.[42] This holding is more than just a victory regarding personal autonomy; it empowered patients and research participants by recognizing their right to consent to or to reject a medical procedure.

Case law continues to develop as the courts must determine, in an ever-changing research environment, what protection is afforded to research participants even under the Common Rule. Recently, state courts in California, Arizona, and the United States Court of Appeals for the Eighth Circuit have addressed the issue of informed consent in research studies.[43] The California Supreme Court held that not disclosing material facts and conflicts of interest in research studies is a breach of fiduciary duties.[44] The Arizona Court of Appeals discussed the informed consent required if secondary biospecimens[45] are going to be used

(examining the legality of performing more research on human blood without gaining additional consent of the participants); Moore v. Regents of the Univ. of Cal., 793 P.2d 479, 483 (Cal. 1990) (recognizing the patient had a cause of action for breach of fiduciary duty because the research doctor did not disclose material facts of the research study); Schloendorff v. Soc. of N.Y. Hosp., 105 N.E. 92, 93 (N.Y. 1914) (recognizing the significance of informed consent).

37. *Schloendorff*, 105 N.E. at 93; Laura B. Rowe, *You Don't Own Me: Recommendations to Protect Human Contributors of Biological Material After* Washington University v. Catalona, 84 CHI.-KENT L. REV. 227, 234 (2009) (discussing the significance of the judicial recognition of informed consent).

38. *Schloendorff*, 105 N.E. at 93.

39. *Id.*

40. *Id.*

41. *Id.*

42. *Id.* ("Every human being of adult years and sound mind has a right to determine what shall be done with his own body . . . .").

43. *See supra* note 36 (describing recent case law in multiple jurisdictions concerning the Common Rule protections to human subjects).

44. Moore v. Regents of the Univ. of Cal., 793 P.2d 479, 483 (Cal. 1990).

45. Havasupai Tribe v. Ariz. Bd. of Regents, 204 P.3d 1063, 1067 (Ariz. Ct. App. 2008).

for a different study than that disclosed.[46] Finally, the Eighth Circuit held that there is no additional consent needed if the researchers want to give secondary biospecimens to a third party because no ownership interest is maintained by the original participant.[47] These cases show that despite there only being one regulation for human subject testing, different jurisdictions have interpreted and applied the law of secondary biomaterials and informed consent in very different ways.

Sadly, it is the controversies regarding ethical research, not the case law, which have proven to be the most influential reasons for reform.[48] The most infamous ethical violation in American history took place in Macon County, Alabama in 1932.[49] The U.S. Public Health Service designed a study to observe the long-term effects of untreated, latent syphilis in black males.[50] These men were told they had "bad blood" and their syphilis remained untreated even after Penicillin became widely available in the 1950's.[51] This study continued until 1972 when a panel found that the study was unethical and that the men should be given the treatment immediately.[52] Aside from the withholding of treatment, these men were subject to spinal taps and other examinations to measure the incidence of neurosyphilis.[53] This study was a major catalyst for the Belmont Report, which was

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46. *Id.* at 1067–68. Here, researchers were studying the blood samples beyond what the informed consent form detailed they would do. *Id.* at 1066–67. This was especially meaningful to the Havasupai tribe because blood has a spiritual meaning in their culture. Katherine Drabiak-Syed, *Lessons from* Havasupai Tribe v. Arizona State University Board of Regents*: Recognizing Group, Cultural, and Dignitary Harms as Legitimate Risks Warranting Integration into Research Practice*, 6 J. HEALTH & BIOMEDICAL L. 175, 214 (2010); Amy Harmon, *Tribe Wins Fight to Limit Research of Its DNA*, N.Y. TIMES, Apr. 22, 2010, at A1. Arizona State University later settled with the Havasupai tribe to pay $700,000 to forty-one of the Tribe's members. *Id.* Additionally, the tribe members were given back the leftover blood samples. *Id.*

47. Wash. Univ. v. Catalona, 490 F.3d 667, 673–74 (8th Cir. 2007).

48. *See infra* notes 56–74 and accompanying text (discussing recent research controversies that have led to reforms in the current Common Rule).

49. Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, 8 HASTINGS CTR. REP., Dec. 1978, at 21, 22.

50. *Id.*

51. *Id.* at 21, 24; *Penicillin: Opening the Era of Antibiotics*, U.S.D.A. AGRIC. RES. SERV., https://www.ars.usda.gov/midwest-area/peoria-il/national-center-for-agricultural-utilization-research/docs/penicillin-opening-the-era-of-antibiotics/ [https://perma.cc/9PQ8-9KZN].

52. Brandt, *supra* note 49, at 21, 26. One important point is that researchers did not infect any of the men with syphilis. Rather, the researchers failed to intervene with the acceptable treatment to prevent the spread and worsening of the disease. *Id.* at 22.

53. *Id.* at 23. Neuro-syphilis is an advanced syphilis infection where the disease spreads to the brain and nervous system. Richard P. Knudsen, *Neurosyphilis Overview of Syphilis of the CNS*, MEDSCAPE (June 15, 2016), http://emedicine.medscape.com/article/1169231-overview [https://perma.cc/5G7R-N6GL].

written only two years later.[54] The Tuskegee Syphilis study remains a constant reminder to bioethicists of the dangers of rules that are too lax or that do not properly protect the rights of human subjects.[55]

Another infamous story concerns a young African-American woman who was diagnosed with an aggressive cervical cancer at Johns Hopkins in 1951.[56] Henrietta Lacks's cancerous cells were unique because they had the ability to survive and multiply in a culture sample.[57] Henrietta died eight months after her diagnosis, but her cells continued to divide and thrive in a laboratory setting.[58] Henrietta's husband orally consented to the harvesting of his wife's cells, but only after the researchers promised to give him the results of their findings.[59] These "HeLa" cells, named for Henrietta Lacks, are still used in research today because of their ability to survive in a cell culture.[60] The "HeLa" cells helped researchers achieve major breakthroughs, but the Lacks family was never informed of the continued uses of the cells, nor did they share in the financial windfall derived from these rare cells.[61] The publications related to the "HeLa" cells illustrate not only research misconduct, but also a research community that tolerates these actions.[62] Neither the peer-reviewed journals that published the genome nor the conferences that hosted these scientists raised questions concerning the informed consent of the patient.[63] These "HeLa" cells were harvested before the promulgation of the Common Rule, but scientists continue to use these cells under the current regulatory framework outlined by the Common Rule.[64]

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54. Belmont Report, 44 Fed. Reg. 23, 192 (Apr. 18, 1979).

55. *A Cautionary Reminder: Nuremberg Revisited*, ETHICS IN HEALTH (June 7, 2013), http://ethicsinhealth.org/?p=463 [https://perma.cc/666J-ZZSK].

56. Rebecca Skloot, *The Immortal Life of Henrietta Lacks, the Sequel*, N.Y. TIMES, Mar. 23, 2013, at SR4. [hereinafter Skloot, *The Immortal Life of Henrietta Lacks*]; Rebecca Skloot, *Henrietta's Dance*, JOHNS HOPKINS MAG. (Apr. 2000), http://pages.jh.edu/jhumag/0400web/01.html [https://perma.cc/QG5T-5M3T] [hereinafter Skloot, *Henrietta's Dance*].

57. *See* Skloot, *Henrietta's Dance*, *supra* note 56 (detailing the characteristics of Henrietta Lacks' cancer cells).

58. *Id.*

59. *Id.*

60. *Id.*

61. *Id.*

62. *See* Skloot, *The Immortal Life of Henrietta Lacks*, *supra* note 56, at SR4. ("The publication of the HeLa genome without consent isn't an example of a few researchers making a mistake. The whole system allowed it.").

63. *Id.*

64. *See supra* notes 60–61 and accompanying text (discussing that HeLa cells were continuously used without additional consent well after the promulgation of the Common Rule in 1991).

Ethical violations continue to occur under the current Common Rule, and sometimes these ethical violations lead to death. In 1999, Jesse Gelsinger was eighteen years old when he died as a result of the drug dosage he received in a clinical trial.[65] Despite his previous health conditions rendering him a poor candidate for the study, he was admitted to participate.[66] Jesse's death would be the first death as a result of gene therapy.[67] After Jesse's passing, it was discovered that the lead researcher, Dr. James Wilson, had a significant financial conflict of interest.[68] The prior Common Rule had no provisions directly addressing whether financial conflicts of interests for investigators and research institutions must be disclosed to research participants.[69]

The Common Rule failed to protect the Lacks family or the Gelsinger family. These are only two tragic stories of the failure of the previous Common Rule to protect research participants. There are other ethical violations that show the same conclusion.[70] The research community was in great need of guidance in this area.

C. Regulation and Reform

While medical research is ever-evolving, the regulation of such research has been slow-moving and mostly reactionary.[71] The Food and Drug Act of 1938 was the first piece of U.S. legislation that addressed the regulation of human subjects in research.[72] This statute required a pharmaceutical drug to be proven safe before it could be sold on the market.[73] In an effort to prove the

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65. Robin Fretwell Wilson, *The Death of Jesse Gelsinger: New Evidence of the Influence of Money and Prestige in Human Research*, 36 AM. J.L. & MED. 295, 298 (2010).

66. *Id.* Jesse had a rare disease called ornithine transcarbamylase deficiency that, at the time, was being controlled by diet and medication. *Id.* While he was mostly healthy, his disease put him in a coma the December before he enrolled in the study. *Id.*

67. *Id.* at 301.

68. *Id.* at 298–99, 308. Dr. Wilson had stock in Genovo, a biotech company, at a value of at least $28.5 million. *Id.* at 308.

69. Jennifer A. Henderson & John J. Smith, *Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls*, 57 FOOD & DRUG L.J. 445, 448 (2002) ("[W]hat is most striking about the Common Rule is what is lacking, namely provisions addressing financial conflict of interest for investigators and institutions conducting medical research with human subjects.").

70. *E.g.*, L. McGoey & E. Jackson, *Seroxat and the Suppression of Clinical Trial Data: Regulatory Failure and the Uses of Legal Ambiguity*, 35 J. MED. ETHICS 107, 107–08 (2009) (recounting the case of teenagers that were given antidepressants without being warned that the drug could exacerbate suicidal tendencies).

71. Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 24, 54 (1993); Sparks, *supra*, note 19 (outlining some of the most influential statutory and historical events leading to increased regulation in human experimentation).

72. Sparks, *supra* note 19.

73. *Id.*

safety of their drugs, pharmaceutical companies began clinical trials using human subjects.[74] While the Food and Drug Act established a need for human subjects, it provided no procedural safeguards to ensure the well-being and rights of those participants.[75] Without any safety protocol, these individuals were left to the mercy of their researchers.

The next significant piece of legislation to address the protection of human subjects, the Belmont Report, was promulgated over forty years after the Food and Drug Act of 1938.[76] The Belmont Report was passed in response to the 1974 National Research Act.[77] The 1974 National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[78] In February 1976, the Commission held a four-day conference in an attempt to summarize the basic ethical principles of human testing. The findings from this conference were later condensed into the Belmont Report.[79]

The Belmont Report is composed of three basic ethical principles: respect for persons, beneficence, and justice.[80] These principles are discussed in great length within the Belmont Report. Respect for persons is composed of two ethical elements: (1) participants deserve autonomy, and (2) if the participant has diminished capacity, he or she deserves more stringent protection.[81] Respect for persons as an ethical principle paved the way for the Common Rule's informed consent requirements.[82] The rationale was that if a researcher respects the individual and their autonomy, the researcher would never perform an experiment without allowing the individual to make the informed decision to voluntarily participate.[83] Beneficence is the idea that a researcher has ethical duties beyond just strict obligations.[84] The Belmont Report defines beneficence as a combination of not harming the

74. *Id.*

75. Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938).

76. Belmont Report, 44 Fed. Reg. 23,192 (Apr. 18, 1979).

77. *Id.*

78. National Research Act of 1974, Pub. L. No. 93-348, § 201, 88 Stat. 342, 348.

79. Belmont Report, 44 Fed. Reg. at 23,192.

80. *Id.* at 23,193.

81. *Id.* The Belmont Report further defines an autonomous person as "an individual capable of deliberation about personal goals and of acting under the direction of such deliberation." *Id.*

82. Brigid C. Welsh, *Regulatory Overlap and the Common Rule: Redefining Research on Human Subjects and Quality Improvement*, 43 U. MEM. L. REV. 847, 854–55, 859–60 (2013).

83. Belmont Report, 44 Fed. Reg. at 23,193.

84. *Id.* at 23, 194.

patient and maximizing the possible benefits while minimizing the risks.[85] As discussed in Part II.A, the Hippocratic Oath provides that a doctor or researcher should "do no harm."[86] That idea was incorporated into the Belmont Report through beneficence.[87] Justice is the final of the three components of the Belmont Report. Justice is composed of five formulations: to each person (1) "an equal share," (2) "according to individual need," (3) "according to individual effort," (4) "according to societal contribution," and (5) "according to merit."[88]

Less than twenty years after the passage of the Belmont Report, it became clear its principles were not providing adequate protection to human subjects.[89] While the Belmont Report introduced applications that are still relevant to the Common Rule today, such as informed consent, assessments of risks and benefits, and selection of participants, the overall impact of the Report was insufficient to properly protect human research subjects.[90] With the promulgation of the Common Rule, HHS borrows many of the concepts from the Belmont Report and addresses the concept in the same way. For example, when policymakers drafted the Common Rule, they maintained many of the original definitions from the Belmont Report.[91] The Common Rule was passed in 1991.[92] This policy has been in effect, with little modification, since the time of the passage.[93] Recent issues concerning the Common Rule have led lawmakers and researchers to question whether the Common Rule is still relevant.[94] While the passage of amendments to the Common Rule is significant, the basic structure of the Common Rule remains the same. Because of this, it is imperative to have an understanding of the Common Rule even prior to the Final Rule. The regulatory framework of the

85. *Id.*

86. *Id.*; *see supra* Part II.A.

87. Belmont Report, 44 Fed. Reg. at 23,194.

88. *Id.*

89. Gerald S. Schatz, *Are the Rationale and Regulatory System for Protecting Human Subjects of Biomedical and Behavioral Research Obsolete and Unworkable, or Ethically Important But Inconvenient and Inadequately Enforced?*, 20 J. CONTEMP. HEALTH L. & POL'Y 1, 4–7 (2003) (explaining the criticisms of the Belmont Report).

90. *Id.* at 6–7, 12.

91. For example, the Belmont Report defines research as "an activity designed . . . to develop or contribute to generalizable knowledge." Belmont Report, 44 Fed. Reg. at 23,193. The Common Rule, on the other hand, defines research as "a systematic investigation . . . designed to develop or contribute to generalizable knowledge." 45 C.F.R. § 46.102(d) (2005).

92. 45 C.F.R. § 46.101; *see also Federal Policy for the Protection of Human Subjects*, *supra* note 7 (identifying 1991 as the publication date of the Common Rule).

93. Welsh, *supra* note 82, at 863.

94. *Id.* at 862–63.

Common Rule will be extensively dissected and analyzed in the following section.

III. THE ANATOMY OF THE ORIGINAL COMMON RULE

The Common Rule was enacted in 1991, codified by fifteen different federal departments and agencies, and amended in 2005.[95] There are two main protections afforded by the Common Rule: informed consent by the patient and the IRB requirements.[96]

A. Introduction to the Regulatory Framework

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 Federal departments and agencies."[97] The Common Rule applies to all research involving human subjects "conducted, supported or otherwise subject to regulation" by a federal agency or an agency that undertakes to do appropriate research.[98] Although the Common Rule is codified in different statutes for each of the fifteen federal agencies that enforce the rule, the language of the statute is universal.[99]

The Common Rule begins with relevant definitions, but, as discussed later in this Comment, these definitions provide ample questions and confusion.[100] Under the Common Rule, a human specimen, as defined by the statute, is a "living individual" from whom the researcher obtains "data through intervention" or "identifiable private information."[101] No portion of this definition refers to whether a human specimen's secondary biospecimens are protected under the Common Rule. Research is defined as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[102] With scientific research advancing rapidly, many definitions in the Common Rule do not provide enough information on what is or is not included within them.

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95. *Federal Policy for the Protection of Human Subjects*, *supra* note 7.

96. 45 C.F.R. §§ 46.101, 109, 116.

97. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,935 (Sept. 8, 2015).

98. 45 C.F.R. § 46.101(a).

99. *See Federal Policy for the Protection of Human Subjects*, *supra* note 7 (listing the federal agencies, as well as providing website links to the Agencies' websites that are compliant with the Common Rule).

100. 45 C.F.R. § 46.102.

101. *Id.* § 46.102(f).

102. *Id.* § 46.102(d).

B. Informed Consent

Informed consent is premised on the idea that a researcher may not perform research on a human subject unless that human subject has given "legally effective informed consent."[103] This informed consent must provide the prospective participant a sufficient opportunity to consider his or her participation without undue coercion or undue influence.[104] Coercion can be positive, such as a professor offering students that participate in a study extra credit, or negative, such as threatening patients.[105] Neither positive nor negative coercion is allowed.[106]

The informed consent document must be printed in a language that the participant will understand and cannot include exculpatory language that will limit the participant's rights.[107] In addition to the procedural requirements, the Common Rule requires certain substantive elements to be present in every informed consent document such as: an explanation of the purposes of the research study, the reasonably foreseeable risks, any foreseeable benefits to the study, and who the participant may contact for questions.[108] In certain unique situations, the Common Rule imposes additional elements.[109] Under the current regulation, there is no informed consent required for biospecimens, such as internal organs and blood samples, and other human byproducts, such as stem cells and tumors.[110]

While participants often must sign an informed consent document before participating in a study, informed consent continues throughout the research and can be withdrawn at any

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103. *Id.* § 46.116.

104. *Id.*

105. *See, e.g.*, *MSU Denver Students as Research Subjects*, METROPOLITAN ST. U. INSTITUTIONAL REV. BOARD, http://www.msudenver.edu/irb/guidance/studentsasresearch subjects/ [https://perma.cc/FU9M-UC88].

106. *Id.*; 45 C.F.R. § 46.116.

107. 45 C.F.R. § 46.116; Zulfiqar A. Bhutta, *Beyond Informed Consent*, 82 WHO BULL. 771, 772 (2004), http://www.who.int/bulletin/volumes/82/10/771.pdf [https://perma.cc/9LSD-PS94]. This means that the informed consent must be written in a language that the patient will understand, regardless of what language the researchers use. *See id.* at 772, 774 ("[I]nformed consent forms are also usually designed in developed countries, translated and then back-translated to ensure that they retain their original meaning.").

108. 45 C.F.R. § 46.116(a)(1)–(8).

109. *Id.* § 46.116(b). These additional elements include: the approximate number of participants, termination of participation guidelines, any additional costs that the participant can expect, the consequences of withdrawing during the research, and the statement that there may be some risks that are unforeseeable by the researchers. *Id.*

110. *See id.* § 46.116 (providing the elements of informed consent, none of which cover additional human specimens); *id.* § 46.102(f) (defining the term human subject with no direction as to other protected human materials).

time for any reason.[111] If the human subject chooses to resign from the study, they cannot be penalized in any way.[112]

C. The Role and Procedures for the Internal Review Board

IRBs, and the role that IRBs serve in the research setting, are the second main issue addressed in the Common Rule.[113] IRBs must approve the research methods and the informed consent documents prior to the start of the study.[114] The Common Rule mandates that each IRB be composed of at least five members, with varying backgrounds to account for a complete and adequate review of the proposed research.[115] Members of the IRB should be qualified through experience and expertise, and all IRBs should have a diversity of members.[116] Special consideration should be given when the research will be conducted on historically vulnerable groups.[117] An IRB may not have members of only one sex.[118] Furthermore, an IRB must have at least one member whose primary concern is nonscientific, and at least one member whose primary concern is scientific.[119] Finally, each IRB must have at least one member that is disaffiliated from the institution conducting the research.[120] These requirements for the composition of the IRB promote objective review of research protocols, which allows IRBs to better serve the human subjects involved in the proposed studies.[121] Theoretically, the more diverse an IRB is, the more effective the IRB is.

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111. *Id.* § 46.116(a)(8).

112. *See id.* ("[T]he subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."); *see also* Office of Human Research Protections, *Withdrawal of Subjects from Research Guidance*, U.S. DEPT. OF HEALTH & HUMAN SERVICES (2010), http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-withdrawal-of-subject/index.html [https://perma.cc/2D8T-XXC9]. Examples of penalties include barring the patient from receiving any further healthcare services from that facility or that the former participant must reimburse the study for their costs.

113. 45 C.F.R. § 46.107 (2005).

114. *Id.* § 46.109.

115. *Id.* § 46.107(a).

116. *Id.* Diversity should be evaluated with consideration of the members' gender, race, cultural backgrounds, and should reflect the attitudes of the community. *Id.* Additionally, if there are any specific concerns with particular sensitivities that should be addressed with the diversity of the IRB. *Id.*

117. *Id.* § 46.107(a). Historically vulnerable groups in the research context are children, prisoners, pregnant women, or handicapped or mentally disabled people. *Id.*

118. *Id.* § 46.107(b). This is aimed at ensuring that no decision reached by the IRB is on the basis of purely gender preferences. *Id.*

119. *Id.* § 46.107(c).

120. *Id.* § 46.107(d). This disaffiliated person must not be the family member of someone affiliated with the institution. *Id.*

121. *Id.* § 46.107(a).

The IRB performs many important tasks, such as overseeing and approving the research plan to be followed during the human experimentation, as well as the informed consent document research participants sign.[122] The IRB has three written procedural requirements for regulating the research performed at the institution. First, the IRB conducts its initial and continual review before reporting its findings and actions to the investigator and the institution.[123] The IRB determines which research projects will require review more often than annually and which projects will need a follow-up.[124] In addition to follow-up, the IRB verifies that there have been no major changes to the research procedure or otherwise since the previous IRB review. [125] Finally, the IRB must ensure there is prompt reporting to the IRB by the researchers of any proposed changes in the research activity.[126] Generally, additional IRB review should not be initiated unless it has become necessary to prevent harm to human life.[127] The IRB must further create written procedures to ensure that there is prompt reporting to the IRB, appropriate institutional officials, and the department or agency head if any unanticipated problems arise or there is any suspension of IRB review.[128] Unless the research activity is subject to expedited review,[129] the IRB reconvenes for meetings to review the proposed research, and the majority of the IRB members must be present for these meetings.[130] At least one of the IRB members present cannot have the scientific aspects of the study as his or her primary concern.[131]

Under certain circumstances as prescribed by the Common Rule, a research project can undergo expedited review, rather than a full review by the IRB.[132] Expedited review is available for certain types of research "involving no more than minimal risk."[133] The HHS secretary has posted a list of categories of research

122. *Id.* § 46.109.
123. *Id.* § 46.103.
124. *Id.*
125. *Id.*
126. *Id.* §§ 46.103(b)(4), 46.108(b).
127. *Id.*
128. *Id.* § 46.103(b)(5).
129. *See infra* notes 137–39 and accompanying text (providing the definition of expedited review and giving examples of when expedited review may be appropriate, as distinguished by the Common Rule).
130. 45 C.F.R. § 46.108(b).
131. *Id.*
132. *Id.* § 46.110.
133. *Id.*

where expedited review can be employed.[134] This list is subject to change after the agency has had an opportunity to review the request for expedited review.[135] Aside from the activities listed by the HHS, the IRB may use expedited review for minor changes that had been previously approved by the IRB.[136] The IRB should provide procedures and methods to ensure all members are advised of research proposals.[137] During expedited review, either the IRB chairperson or one or more experienced reviewers as designated by the chairperson can carry out the review.[138] Finally, the department or agency may choose to restrict, suspend, or terminate the institution's use of the expedited review.[139] Expedited review is an issue addressed in the Final Rule.[140] These changes will be further discussed in Part V.

The Common Rule has attempted to protect human subjects by requiring the informed consent provisions for human subjects and IRBs.[141] Informed consent and IRBs are vital to the protection of human subjects, but the recent advancements in medicine have warranted the need to revise the current regulation.[142] Under the proposed NPRM, published in the Federal Register on September 8, 2015, the Common Rule would be updated for the first time in over ten years.[143] The next section will discuss the driving forces

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134. *Id.*; OFFICE FOR HUMAN RESEARCH PROTECTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, OHRP EXPEDITED REVIEW CATEGORIES (1998) https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html [https://perma.cc/9H4X-EJB5]. The clinical categories listed as of January 2016 included: (1) clinical studies involving: (i) research on drugs for which there was no investigational new drug application, or (ii) research on medical devices where there is either no requirement for an investigational exemption application or the medical device is cleared for marketing and will be used in accordance with that clearance; (2) collection of blood samples by finger stick, heel stick, ear stick, or venipuncture; (3) prospective collections of biospecimens for research purposes by noninvasive means; (4) collection of data through noninvasive procedures, such as x-rays; (5) research involving materials that have been collected, or will be collected for non-research purposes; (6) collection of data from voice, video, digital, or image recordings; (7) research on individual or group characteristics, such as perception, cognition, motivation, etc.; (8) continued review of research previously approved by the IRB; (9) any other research that the IRB has determined is no more than a minimal risk and no additional risks have been identified. *Id.*

135. 45 C.F.R. § 46.110(a) (2005).

136. *Id.* § 46.110(b).

137. *Id.* § 46.110(c).

138. *Id.* § 46.110(b).

139. *Id.* § 46.110(d).

140. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7171–72 (Jan. 19, 2017).

141. *See supra* Part III.B–C (discussing the current regulatory framework under the Common Rule).

142. Welsh, *supra* note 82, at 851–52.

143. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,933 (Sept. 8, 2015).

behind the changing research environment and the need for a revision to the Common Rule that led the implementation of the Final Rule.

IV. THE NEED FOR CHANGE

As discussed in Part II.C, recent case law and ethical violations highlight the growing need for regulatory change. HHS remarked that since the promulgation of the Common Rule, "the landscape of research activities has changed dramatically, accompanied by a marked increase in . . . research."[144] A change in how research is conducted has led to incorporating new technologies such as "imaging, mobile technologies, and the growth in computing power."[145] A combination of the changing research environment and the increase in the magnitude of scientific research catalyzed the need for the ANPRM in 2011.[146] The ANPRM put the public on notice of the Office for Human Research Protections (the "OHRP," a department within HHS) and HHS' plan to amend the Common Rule.[147] The summary of this ANPRM called for "comment on how current regulations for protecting human subjects who participate in research might be modernized and revised to be more effective."[148] At the end of the comment period on September 26, 2011,[149] interested parties had submitted approximately 1,100 comments.[150] The Office of Science and Technology Policy and HHS then attempted to incorporate new changes that would provide better protection for human subjects.[151] Armed with these comments, HHS did not publish the NPRM of the Common Rule in the Federal Register until September 8, 2015.[152] When proposing changes to the Common

144. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44513 (July 26, 2011) (codified at 45 C.F.R. pts. 46, 160 and 164; 21 C.F.R. pts. 50 and 56).

145. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,938.

146. *See* Barbara J. Evans, *Why the Common Rule is Hard to Amend*, 10 IND. HEALTH L. REV. 365, 366, 371–75 (2013) (discussing the ANPRM's reform agenda).

147. *Id.* at 371–72.

148. Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,512.

149. *Id.* at 54, 408.

150. *See* Evans, *supra* note 146, at 374 (detailing the number of comments submitted for consideration in response to the ANPRM).

151. Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,512.

152. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,933 (Sept. 8, 2015).

Rule in the NPRM, the Belmont Report's three principles of respect for persons, beneficence, and justice remained the foundation for the ethical considerations.[153] Finally, on January 19, 2017, the Final Rule was published, noting that "[e]volving technologies, and the growth in computing power – have changed the scale and nature of information collected," when justifying the rationale for modernizing the Common Rule.[154]

A. Reasons for Modifying the Common Rule

Changes to the Common Rule were needed to promote the general safety and welfare of human subjects.[155] Jerry Menikoff, the current Director of the OHRP, stated that changes to the Common Rule were necessary because "[t]he way we do research has changed," due to the "massive amounts of data" to be collected.[156] Menikoff explained that the two primary goals of the changes in the proposed rule were to: (1) better protect human subjects to the extent that it is needed, and (2) reduce burdens, delays, and ambiguities so researchers can continue their research.[157]

B. Three Major Changes

The major changes of the proposed Common Rule can be reduced to three overarching categories: (1) informed consent, (2) IRB activities and procedures, and (3) de-identified biospecimens. The NPRM sought to make the informed consent documents more understandable and applicable to the research study that the potential human subject will be participating in.[158] The NPRM also sought to streamline the IRB process, allow for more expedited review in research studies with minimal risk, and require a single IRB for research studies located at multiple facilities.[159] Finally, the NPRM proposed expanding the definition

153. *See id.* at 53,940; *see also supra* notes 87–92 and accompanying text (providing an overview of the three underlying ethical principles of the Belmont Report).

154. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7151 (Jan. 19, 2017).

155. *See supra* notes 101–02 and accompanying text (discussing specific examples where the Common Rule does not provide protection for human tissues and biospecimens).

156. *See* Jerry Menikoff, Director, Office for Human Research Protections, Transcript of Town Hall Meeting on Common Rule NPRM, (Oct. 20, 2015) http://www.hhs.gov/ohrp/humansubjects/regulations/transcriptoct20townhall.html [https://perma.cc/TVY3-AMLL].

157. *Id.*

158. *See infra* notes 161–76 and accompanying text (outlining the changes to the Common Rule's informed consent requirements).

159. *See infra* notes 177–86 and accompanying text (describing the changes to the IRB protocol under the proposed changes in the NPRM).

of "human subject" in the Common Rule to include secondary biospecimens.[160] Each of these three categories and their proposed changes will be addressed individually.

1. Informed Consent. Both informed consent and how researchers obtain this informed consent are important changes to the Common Rule.[161] The methods of human subject testing have changed significantly since the promulgation of the Common Rule, so updating informed consent could increase patient awareness of study risks and promote transparency among institutions.[162]

The first proposed major change to informed consent was the use of blanket informed consent documents.[163] Blanket consent forms, which are permissible under the Common Rule, are designed for all patients and do not address the particular circumstances and concerns of the participant actually signing the consent form.[164] Many regulators felt that these informed consent documents had become too complicated and failed to inform patients of the risks specific to their trials.[165] The documents were "unduly long" and tended to be confusing to those not familiar with the technical vocabulary.[166] Informed consent documents appeared to serve more as exculpatory clauses from legal liability than to inform the patient of potential risks during the trial. The NPRM sought to establish a "reasonable person" standard to ensure that the patients are adequately informed.[167] The idea was to shift informed consent from a protection for the facility to a protection of the patient.[168] In the raw, the goal of an informed

160. *See infra* notes 187–205 and accompanying text (detailing the inclusion of secondary biospecimens to the definition of "human subjects" in the Common Rule).

161. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936 (Sept. 8, 2015); Menikoff, *supra* note 156.

162. *See* ERIN D. WILLIAMS, CONG. RESEARCH SERV., RL32909, FEDERAL PROTECTION FOR HUMAN RESEARCH SUBJECTS: AN ANALYSIS OF THE COMMON RULE AND ITS INTERACTIONS WITH FDA REGULATIONS AND THE HIPAA PRIVACY RULE 12–16 (2005), http://www.fas.org/sgp/crs/misc/RL32909.pdf [https://perma.cc/8TAH-LW56]; Rowe, *supra* note 37, at 247–48.

163. *Id.*

164. Henry T. Greely, *The Uneasy Ethical and Legal Underpinnings of Large-Scale Genomic Biobanks*, 8 ANN. REV. GENOMICS & HUM. GENETICS 323, 358 (2007).

165. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936 (Sept. 8, 2015); Menikoff, *supra* note 156 ("There are complaints that consent forms are particularly in clinical trials, complicated clinical trials, they can be very long, very complicated, some people would suggest that they are too long and too complicated.").

166. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,936.

167. Menikoff, *supra* note 156 ("So some of the changes will require the document to provide essential information that a reasonable person would want to know.").

168. *Id.* ("[O]ften some people think it's often lawyers trying to protect the institution . . . that's more helpful in terms of protecting institutions as oppose[d] to the goal of genuinely doing a good job in terms of informing the subject.").

consent document is to allow the patient to make a well-informed decision about whether to participate in the trial based on the risks and that patient's personal history.[169] With this in mind, the NPRM proposed a relatively short "core" consent form that would contain information specific to the patients and the study methods.[170] The informed consent document still needed to conform to the original requirements, such as being organized and clear and being printed in a language the participant can understand, but the important information could no longer be "buried and hard to find."[171] In addition to this core consent form, the facility may attach more detailed consent information using appendices should they feel they need to provide more relevant risk information.[172] HHS believed this posting requirement would serve as a means of enforcement because the drafters of informed consent documents would draft the forms knowing they will be posted and reviewed.[173]

The NPRM also prioritized informed consent in relation to the overall transparency of the institution by requiring researchers who are no longer recruiting participants for their study to publish a final consent form on a public government forum (likely a website), which HHS proposed promotes accountability and transparency.[174] In increasing the standards of informed consent, the proposed changes to the rule seek to empower patients and increase the transparency of the research study to the public.[175] The institution will only need to post one informed consent document, regardless of the number of participants, or the number of sites at which the study will occur.[176]

2. The IRB. The NRPM proposed two main changes to IRB reviews and procedures. The first change addressed the requirements of continued IRB review in low-risk research

169. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,936. HHS's goal is to restructure informed consent "to better assure that subjects are appropriately informed before they decide to enroll in a research study." *Id.*

170. *Id.* at 53,936; Menikoff, *supra* note 156.

171. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,936 ("Consent forms would no longer be able to be unduly long documents, with the most important information often buried and hard to find."); Menikoff, *supra* note 156.

172. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,970; Menikoff, *supra* note 156.

173. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,936.

174. *Id.* at 53,978. The purpose of this rule to subject anyone writing an informed consent document to be "subject to public scrutiny." *Id.* at 53,936.

175. Menikoff, *supra* note 156 ("Why are these secret? Let's open that up a bit and it will lead to better consent form[s]. That's the premise here.").

176. *Id.*

studies.[177] The second sought to streamline cooperative research by mandating that research institutions engaged in cooperative research within the United States would be subject to one IRB.[178] For example, one medical school may have many campuses and each campus may be participating in a trial. The NPRM strongly suggested that the single IRB should be one unaffiliated with the institutions.[179] Under the prior Common Rule, IRBs could be located at each research site, whereas under the proposed changes of the NPRM, one single IRB would review all actions of the research study regardless of the different campuses. Finally, HHS proposed that a new category of activities, referred to as "exempt," would be established.[180] Researchers would be able to use online tools to ascertain whether their research would be exempt, excluded, or subject to the Common Rule.[181]

The NPRM also proposed changes to the continuing review process.[182] The proposals would have eliminated continuing review in instances where the study has undergone expedited review, or if the study did not undergo expedited review but there is no longer the need for continued review during the investigation.[183] If the risk of harm to the individuals was low, the IRB would not need to conduct continued review of the research study. The rationale underlying this change was to allow the resources and time of the IRB to be allocated to other potentially more harmful research activities. This would also promote efficiency because researchers would not need to wait on IRB review for low-risk studies. If the IRB reviewer felt that there should be continued review, he or she could override this and continue review.[184] The IRB reviewer would need to document the reason why he or she chose to override this standard and continue to document the reviews.[185] IRBs play an essential role in research development, and a more efficient

177. *Id.* at 53,936.

178. *Id.* at 53,982 ("The Common Rule currently requires that each institution engaged in a cooperative research study obtain IRB approval of the study, although it does not require that a separate local IRB at each institution conduct such review. In many cases, however, a local IRB for each institution does independently review the research protocol . . . .").

179. *Id.* at 53,937.

180. *Id.* at 53,936.

181. *Id.*

182. *See infra* notes 183–86 and accompanying text (explaining the proposed changes to the continuing review process as discussed in the NPRM).

183. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,937.

184. *Id.* at 53,985 ("[E]liminating continuing review for many minimal risk studies (namely those that qualify for expedited review), unless the reviewer documents why continuing review should take place . . . .").

185. *Id.* at 53,986.

system would allow the IRB to focus on the riskiest research activities and promote the use of less risky means to accomplish study goals.[186]

3. De-Identified Biospecimens. Finally, for the first time, HHS sought to regulate de-identified biospecimens within the Common Rule.[187] Before these proposed changes, de-identified biospecimens were entirely outside the scope of the Common Rule.[188] The NPRM proposed that researchers would need to obtain informed consent to utilize secondary biospecimens "even if the investigator is not being given information that would enable him or her to identify whose biospecimen it is."[189] The NPRM detailed that informed consent would not be necessary for each specific use of a biospecimen, but that should researchers intend to use the biospecimens in the future, they will need to obtain a "broad" consent form.[190]

As mentioned previously in Part III, the prior definition of a human subject in the Common Rule did not include secondary biospecimens at all.[191] For example, if a research participant gave a ten-milliliter sample of blood for a research study and the researchers only need five milliliters, it was unclear whether remaining blood samples became subject to the Common Rule's regulations.[192] As the Common Rule was written prior to the Final Rule, as long as the sample is de-identified, it would no longer be considered a human subject, and thus, is outside the scope of the Common Rule.[193] Furthermore, the changing research environment shows a tendency to perform more experimentation on human biospecimens and tissue samples, rather than on

186. Menikoff, *supra* note 156.

187. *Id.* As a point of clarification, the de-identified biospecimens the Common Rule addresses are within the statutory definition of biospecimens listed in the Common Rule, not the statutory definition of de-identified biospecimens in the Health Insurance Portability and Accountability Act. *Id.*

188. Menikoff, *supra* note 156.

189. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,936.

190. *Id.*

191. *See supra* notes 100–02 and accompanying text (defining the term human specimen under the Common Rule); Russell Korobkin, *Autonomy and Informed Consent in Nontherapeutic Biomedical Research*, 54 UCLA L. REV. 605, 621 (2007) (providing details about the current definition of "human subjects" but excluding any mention of secondary biospecimens).

192. 45 C.F.R. § 46.102(f) (2005). No mention of these secondary biomaterials is listed in the current statute. *Id.*

193. *See id.* There is a very limited definition for what is a human subject and whether the information is individually recognizable. *See id.*

humans themselves.[194] The NPRM requirement for secondary biospecimens was designed to allow the participant to consider how the participant wants his or her biospecimens handled and to consider that his or her biospecimens could be used for something outside the original research study.[195]

The NPRM sought to incorporate de-identified biospecimens into the definition of human subject. HHS proposed two alternatives to including de-identified biospecimens in the definition of human subjects. Under the first alternative (referred to by HHS as "Alternative A"), the definition of human subjects would include whole genome sequencing.[196] Any portion of the human genome that was sequenced would be subject to the Common Rule.[197] HHS believed that Alternative A would "giv[e] greater weight to the principle of beneficence, while giving less weight to the principle of respecting the autonomy of persons."[198] The biggest drawback to using Alternative A, as proposed, was that it would only codify a single technology, limiting the scope of biospecimens under the Common Rule regulations.[199]

Under the second alternative (referred to by HHS as "Alternative B"), only information considered "bio-unique" would be included in the definition of human subjects.[200] HHS conceded that Alternative B is "conceptually very similar" to Alternative A, but would provide a broader scope because more information would be subject to the Common Rule.[201] The biggest predicted drawback of Alternative B, as proposed, was that HHS would need to continually monitor and update which forms of technology would create information subject to this rule.[202]

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194. *See* Lori B. Andrews, *Harnessing the Benefits of Biobanks*, 33 J.L. MED. & ETHICS, 22, 22 (2005); Rowe, *supra* note 37, at 248–49; Rebecca Skloot, *Taking the Least of You*, N.Y. TIMES, (Apr. 16, 2016) http://www.nytimes.com/2006/04/16/magazine/16tissue.html?page wanted=all [https://perma.cc/SED8-DMVF] (detailing the importance of human tissues in developing vaccines, drug tests, and new promising pharmaceutical drugs).

195. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936 (Sept. 8, 2015).

196. *Id.* at 53,945.

197. *Id.*

198. *Id.*; *see also supra* notes 86–90 (discussing the origins of the principles of beneficence and respect for personal autonomy).

199. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. at 53,945.

200. *Id.* at 53,945–46. In order for information to be considered "bio-unique," three conditions would need to be met: (1) would need to be the result of technology capable of producing information unique to a specific individual; (2) enough information would need to be generated that it would be unique to the individual; and (3) there would need to be publically available information that when combined with the technology would result in the possibility that the person could be identified. *Id.* at 53,946.

201. *Id.* at 53,946.

202. *Id.*

Finally, even if secondary biospecimens were considered "unidentifiable" under HIPAA, informed consent from the individual would still be required.[203] In the analogy of the patient who gives a blood sample, if there is left-over blood after testing a blood sample, the patient would need to consent to the use of this remaining blood in any additional studies.[204] This consent could be obtained through the use of a broad consent form prior to the drawing of the blood, which would provide consent for future unknown research.[205]

C. Other Changes to the Common Rule

In addition to these three main categories, there was a pair of secondary proposed changes to the Common Rule.[206] One of these proposals called for the extension of the Common Rule to clinical trials.[207] This was not intended to infringe on the regulation of the FDA over clinical trials, but merely intends to allow for federal oversight if there are clinical trials occurring at a federally funded institution.[208] The second proposal strives to set a ground floor requirement for privacy, such as compliance with HIPAA.[209] While both of these proposals are addressed in the Final Rule, the changes to these additional proposals are beyond the scope of this Comment.[210]

With the NPRM, HHS solicited comments from interested parties concerning the proposed changes to the Common Rule.[211] HHS considered these comments before promulgating the Final Rule.[212] The relevant comments and the provision of the Final Rule will be discussed in the following section.

V. THE FINAL RULE AND COMMENTS ON THE NPRM

In promulgating the Common Rule, HHS was subject to the formal rulemaking requirements of the Administrative Procedure

203. *Id.* at 53,936.

204. *Id.*

205. *Id.*

206. Menikoff, *supra* note 156.

207. *Id.*

208. *Id.*

209. *Id.*

210. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7191–92, 7230–31 (Jan. 19, 2017).

211. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936 (Sept. 8, 2015).

212. 5 U.S.C. § 553(c) (2012).

Act (the "APA").[213] In compliance with the APA, public comments regarding the NPRM were requested and considered.[214] When the comment period ended on January 6, 2016, public and private interested parties had submitted 2,189 comments.[215] The comments generally applauded HHS for attempting to strengthen the protections afforded to human subjects,[216] but some stressed that the NPRM was "written in a way that is extremely hard to follow and uses language throughout more suitable for those experienced in reading and interpreting regulation."[217]

In discussing the Final Rule and the comments, the costs and benefits of the changes must be considered. As published, the benefits, both quantified and non-quantified, outweigh the costs of implementation. Quantified benefits outweigh the quantified costs significantly for the 2017–2026 period for both present value and annualized value.[218] The non-quantified benefits include: improved human subjects protections, enhanced IRB oversight in research projects, and increased uniformity between Common Rule departments and agencies.[219] The only projected

213. The APA applies to all federal agencies when they engage in formal rulemaking. 5 U.S.C. § 551. Because HHS is a federal agency, they must comply with the formal rulemaking requirements of the APA.

214. 5 U.S.C. §§ 553(b)–(c) ("[T]he agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments . . . .").

215. *Federal Policy for the Protection of Human Subjects: Docket Folder Summary*, REGULATIONS, http://www.regulations.gov/#!docketDetail;D=HHS-OPHS-2015-0008 (last visited Oct. 28, 2016). The original comment submission period was set to end on December 7, 2015; however, HHS granted the extension until January 6, 2016. *Id.*

216. Yale Office of the Vice President and General Counsel, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 6, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1749 [https://perma.cc/Z3N3-QJWA] ("In general, we strongly support efforts to enhance the protection of human participants involved in research while improving the effectiveness of the federal system of oversight.") [hereinafter Yale University Comment].

217. University of Chicago Office of the Vice President for Research and for National Laboratories, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects, (Jan. 6, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1554 [https://perma.cc/LEN6-E5GK] [hereinafter University of Chicago Comment]. Other interested parties submitted comments criticizing the NPRM for convoluted language. *See* Washington University in St. Louis School of Medicine, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects, (Jan. 6, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1202 [https://perma.cc/M427-KRX7] ("The document is unnecessarily complex and hard to interpret.") [hereinafter Washington University Comment].

218. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7150 (Jan. 19, 2017).

219. *Id.*

non-quantified cost is the time for consultation and compliance among Common Rule agencies.[220]

This section will analyze the trends of a selected number of interested party comments and decipher how these comments contributed to the Final Rule.[221] This Comment is not inclusive of every comment submitted. The comments discussed in this Comment were selected because they were submitted by well-known research and medical institutions, respected professional organizations, or provided unique insight into the provisions of the NPRM. The selected comments will be discussed by characterizing the comments through the three main topics of discussion: informed consent, IRB review, and the treatment of secondary biospecimens.[222]

A. The Final Rule and Comments on Informed Consent

Approximately 200 comments discussed the proposed "core" consent form.[223] Many interested parties, roughly 140, submitted comments that echoed the concerns of HHS that informed consent documents should be shorter and easier to understand.[224] Interested parties seem to agree that added safeguards are needed to protect patients, especially potentially vulnerable groups.[225] However, approximately thirty-five comments opposed this

220. *Id.*

221. *See infra* note 222 and accompanying text (documenting a number of submitted comments and the trends persistent throughout them).

222. *See supra* notes 158–60 and accompanying text (identifying the three most important categories of changes to the Common Rule as the informed consent changes, the procedural IRB changes, and the treatment and definition of de-identified biospecimens).

223. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7211.

224. Emory University, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Dec. 22, 2015), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-0583 [https://perma.cc/9XDT-THPA] ("Emory strongly agrees with the need to reduce the length of informed consent document, while still providing the information that potential study participants need to make sound decisions.") [hereinafter Emory University Comment]; *see also* Association of American Medical Colleges, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 4, 2017), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1325 [https://perma.cc/J4FT-US3Q] [hereinafter AAMC Comment]; University of California Vice President—Research and Graduate Studies, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 4, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1062 [hereinafter University of California System Comment]; Washington University Comment, *supra* note 217; Yale University Comment, *supra* note 216.

225. *See* AAMC Comment, *supra* note 224, at 17. The Common Rule specifically affords extra protections to pregnant women, neonates, and fetuses, as well as prisoners. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research, 45 C.F.R. §§ 46.203–07 (2005); *see also id.* §§ 46.304–06.

change and argued that the proposed solution in the NPRM does not serve to simplify the document.[226] These parties argue that the length of the informed consent documents is not due to the choices of the research institutions, but rather the pressures from federal and private sponsors to disclose every foreseeable risk from participating in the proposed study.[227] Therefore, the proposed changes will have no effect on the length and complexity of the informed consent documents until the other contributing factors are modified. Further, other institutions argue that the NPRM provides no examples of an ideal informed consent document, thus leaving researchers to guess what type of informed consent is required to be compliant.[228] Finally, some parties provided their own input on how to reduce the complexity of informed consent while promoting better patient understanding.[229] These comments expressed concern that language should not be endorsed for length, but rather for clarity and understandability.[230] For example, Boston University proposed the use of list-style formats for informed consent documents with bullet points delineating the important information that patients need to understand in order to make a well-informed decision on whether to participate in a trial.[231]

The NPRM's broad consent form proposal also garnered significant attention in the submitted comments.[232] Approximately 475 comments opposed the broad consent proposal, largely due to the NPRM's proposal that "some type of consent (broad or specific) would be required for research with nonidentified biospecimens."[233] Only 150 commenters spoke specifically to the idea of a broad consent document.[234] Of those that directly discussed broad consent, even fewer commenters

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226. *See supra* note 224 and accompanying text (outlining the universities and medical associations concerned with the complexity of the consent documents).

227. Yale University Comment, *supra* note 216 ("[I]t is our experience that investigators are pressured by sponsors to be more exhaustive in describing reasonably foreseeable risks . . . .").

228. Washington University Comment, *supra* note 217.

229. Boston University Office of the Provost, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Dec. 23, 2015), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-0597 [https://perma.cc/74QW-VAY6] ("Our recommendation is that the format be changed to a list format with bullet points.") [hereinafter Boston University Comment].

230. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7211 (Jan. 19, 2017).

231. *Id.*

232. *Id.* at 7218.

233. *Id.*

234. *Id.*

spoke to the elements of the broad consent form. Public comments voiced multiple concerns with broad consent, such as the concern for institutions to retain their ability to modify and amend broad consent forms (rather than rely on a federal template) and on whether consent given in a broad consent form would be meaningful.[235]

The Final Rule mandates six major revisions to the requirements of informed consent: (1) new requirements for content, organization, and basic presentation of the informed consent document; (2) the basic and any additional elements of consent; (3) the element of broad consent for the storage, maintenance, and any possible secondary research of biospecimens; (4) changes in the criteria for waivers or alterations to research criteria; (5) new provision for IRBS to approve research on biospecimens without the individual's consent under certain circumstances; and (6) the new requirement to post to a copy of the IRB-approved research consent form to a federal website.[236] The Final Rule removes the language that references oral or written consent. Under the new regulations, all the requirements apply to both oral and written consent.[237]

The Final Rule adopts almost all the proposals of the NPRM that sought to improve and clarify the informed consent document.[238] These requirements will apply to the informed consent document as a whole.[239] The Final Rule adds two elements, in addition to the previous six requirements,[240] which include: a statement that the subject's "biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit," and a statement describing whether "clinically relevant research results . . . will be disclosed to subjects, and if so, under what conditions."

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235. *Id.*

236. *Id.* at 7210.

237. *Id.* at 7211.

238. *Id.* at 7213 ("For example, the final rule adopts the proposed requirement specifying that the information provided in an informed consent form must be presented in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.").

239. *Id.*

240. *Id.* at 7215. The original six requirements for informed consent were: (1) a statement that the project may involve risks that are currently unforeseeable; (2) anticipated circumstances when the subject's participation may be terminated by the investigator; (3) additional costs that may result from participation; (4) procedures and consequences for when the subject withdraws participation; (5) a statement that the subject will be notified of significant, relevant findings; and (6) the total number of subjects in the study. *Id.*

For broad consent, the Final Rule does include an option to obtain broad consent as proposed in the NPRM, but, in response to public comments, has incorporated multiple changes.[241] The Final Rule allows broad consent only for secondary research,[242] but no other type of research. This is the most significant change in the broad consent as proposed in the NPRM. The reason for this deviation is that the Final Rule fails to incorporate the NPRM's proposal that all biospecimens, regardless of identifiability, be subject to regulation under the Common Rule.[243] OHRP believed that allowing researchers to use broad consent will "generally provide increased protection to the autonomy of research subjects."[244] The Final Rule also strengthened and simplified the elements of broad consent in response to the received public comments[245] by including the reasonable person standard discussed in Part IV.B.1. Under this standard, the description must provide "sufficient information to allow a reasonable person to expect that the broad consent would permit the types of research conducted."[246] Lastly, the Final Rule declines to include broad consent templates established by the Secretary of HHS. This allows institutions to create their own, more specific broad consent forms.[247]

In addition to these changes, the Final Rule adopts other informed consent requirements. These changes, however, are more circumstance-specific and remain outside the scope of this Comment.

B. The Final Rule and Comments Regarding IRB Review

By far the most discussed IRB proposal is the use of a single IRB review for cooperative research.[248] Multiple interested parties expressed support for "moving towards the use of a single IRB for domestic multi-site studies,"[249] but felt that "this discretionary

241. *Id.* at 7219.

242. Secondary research, as it relates to broad consent, is defined as: "limited to research using identifiable private information or identifiable biospecimens that are collected for either research studies other than the proposed research or non-research purposes." *Id.* at 7220.

243. *Id.* at 7219.

244. *Id.* at 7220.

245. *Id.* at 7220–21.

246. *Id.* at 7221.

247. *Id.* at 7222.

248. *See* Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,981 (Sept. 8, 2015).

249. Stanford University, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Nov. 18, 2015),

practice is [not] something that should be mandated."[250] The view that there is value in a single IRB review in cooperative research, but HHS has not fully fleshed out the details, is echoed in a significant amount of comments submitted.[251] Vanderbilt University suggested that HHS should not prescribe a single IRB review model in promulgating the Common Rule.[252]

The interested parties appear to be in agreement that, while a single IRB review of cooperative research can be effective, single IRB review should not be mandated.[253] Many institutions, including the American Academy of Medical Colleges, propose HHS utilize an incentive-based program.[254] Further, more research needs to be done to test the value of single IRB review before HHS should issue a mandate.[255] Due to the many implications of cooperative research, a strict mandate in regulating these activities will be far-reaching.[256] HHS should comply with the suggestions of the interested parties and not formalize a mandate for single IRB review of cooperative research. Instead, a transition period should be implemented that would incentivize institutions engaging in cooperative research to use single IRB review. In doing so, HHS could conduct research on the effectiveness of single IRB review before promulgating a stringent rule requiring its use.

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https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-0180 [https://perma.cc/ER3M-MJHW] [hereinafter Stanford University Comment].

250. Brown University, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 6, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1510 [https://perma.cc/G8MD-2DJN] [hereinafter Brown University Comment].

251. *See, e.g.*, Colorado State University, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 4, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1159 [https://perma.cc/Y6D9-LQSJ] (agreeing that using a single IRB review is an effective tool but disagreeing that it should become a mandate). Other research institutions that encouraged HHS not to mandate single IRB review for cooperative research include, but are not limited to: Vanderbilt University, University of Chicago, Boston University, Yale, The University of California System, etc. This is by no means an exhaustive list, but rather demonstrates the extensive list of research universities that disagree with mandating single IRB review.

252. *See* Vanderbilt University, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 5, 2016), https://www.regulations.gov/document?D=HHS-OPHS-2015-0008-1188 [https://perma.cc/JJ9J-7N8T] ("We would also encourage a closer look at prescribing any ONE single IRB model in the regulations.") (emphasis in original) [hereinafter Vanderbilt University Comment].

253. *See* Brown University Comment, *supra* note 250; University of California System Comment, *supra* note 224; Vanderbilt University Comment, *supra* note 252.

254. AAMC Comment, *supra* note 224.

255. *Id.*

256. Vanderbilt University Comment, *supra* note 252.

Cooperative review was one of the most commented on proposals of the whole NPRM with over 300 comments discussing it.[257] The comments were divided: 130 comments supported this proposal and 140 comments opposed it.[258] Additionally, some had mixed views of the proposal.[259] The Final Rule incorporates portions of the NPRM while adjusting for the responses from public comment. Therefore, the Final Rule mandates the NPRM's proposal that cooperative research for which more than a single IRB review is required be exempted from the requirements of § 46.114 to decrease the administrative burden while allowing for the transition to this new model.[260] The Final Rule also adopts a delayed compliance date of three years from publication in the Federal Register. This transition period will assist the research community in achieving this new model.[261]

For continuing review, 120 comments discussed the proposal for elimination of continuing review for minimal risk studies.[262] Of these comments, approximately ninety-five of them supported it and only fifteen opposed this proposal.[263] For expedited review, approximately fifty comments were received.[264] The majority of comments supported this proposal, but some comments requested that the Secretary update the list of expedited review categories more frequently than every eight years.[265] The Final Rule will enact that "continuing review is eliminated for all studies that undergo expedited review, unless the reviewer explicitly justifies why continuing review would enhance protection[s] . . . ."[266] The Final Rule provides that a study will be determined to be minimal risk and eligible for expedited review if the "study only involves activities on the Secretary's list, unless the reviewer determines and documents that the study involves more than minimal risk."[267] IRBs will need to document their rationale when overriding that research should be reviewed under expedited review.[268]

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257. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7208 (Jan. 19, 2017).

258. *Id.*

259. *Id.*

260. *Id.* at 7209.

261. *Id.*

262. *Id.* at 7205.

263. *Id.*

264. *Id.* at 7206.

265. *Id.*

266. *Id.* at 7205. The activities that would qualify for the exemption of continuing review would be: (1) research that already qualifies for expedited review, and (2) research that only requires either data analysis or follow-up clinical data. *Id.*

267. *Id.* at 7206.

268. *Id.*

Overall, the NPRM and the Final Rule show an earnest desire to streamline IRB review and to concentrate the review on high-risk activities.[269] The Final Rule also reflects the incorporation of many concerns the commenters had surrounding the current IRB review.

C. The Final Rule and Comments Discussing De-Identified Biospecimens

Biospecimens, and the handling of such material, is the most controversial proposition in the NPRM.[270] Approximately fifty percent of the commenters mentioned the inclusion of de-identified biospecimens into the Common Rule.[271] Two main issues surround the proposed changes to biospecimens: (1) whether biospecimens should be incorporated into the definition of a human subject, and (2) whether the proposed broad consent documents promote patient autonomy.[272] Each of these issues will be discussed and analyzed based on a selection of submitted comments and the inclusion in the Final Rule.

First, interested parties seemed to strongly oppose the inclusion of de-identified biospecimens into the definition of human subjects.[273] Stanford University made the point that, in regards to biospecimens, "the proposed regulations are widely scattered throughout the NPRM."[274] Many parties asserted that currently usable samples held by institutions would be rendered unusable based off the provisions of the NPRM.[275] Further, parties

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269. Stanford University Comment, *supra* note 249.

270. *See infra* notes 272–93 and accompanying text (detailing many comments and objections to the inclusion of secondary biospecimens in the definition of human subjects).

271. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7164.

272. Menikoff, *supra* note 156.

273. *See infra* notes 274–78 (detailing concerns about the inclusion of de-identified biospecimens in the definition of human subjects). The current definition of a human subject is limited and does not mention de-identified biospecimens. 45 C.F.R. § 46.102(b) (2005). HHS asked for comments specifically on whether they should prescribe an actual definition of biospecimens or to leave them under simply "human subjects." Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936–37 (Sept. 8, 2015).

274. Stanford University Comment, *supra* note 249. Stanford also points out that the NPRM spends about one page, out of almost 128 pages of proposed legislation, describing both alternatives to incorporating de-identified biospecimens into the definition of human subjects. *Id.* The University of Arizona expressed that Alternative A was the better option, but did not provide overwhelming support for either option. University of Arizona, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 5, 2016), http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2015-0008-0602 [hereinafter University of Arizona Comment].

275. Boston University Comment, *supra* note 229; University of Chicago Comment, *supra* note 217.

did not seem amenable to either Alternative A or Alternative B that HHS proposed. Other institutions proposed their own limitations on the incorporation of biospecimens.[276] These changes, a portion of comments argue, would create significant administrative burden and add *de minimis* protections for human subjects.[277] One common concern expressed was that because many of these samples are currently de-identified, if researchers want to continue to use them without running afoul of the proposed rule, researchers would need to re-identify the samples to obtain informed consent.[278] These commenters were not alone in their opinion; 80 percent of the commenters were opposed to this change.[279] Additionally, only 20 commenters explicitly endorsed Alternative A or Alternative B.[280] Some commenters went further and asserted that neither Alternative A, nor Alternative B would "give individuals who wanted to control the use of their biospecimens the opportunity to do so."[281] Overall, approximately 250 commenters (roughly 12 percent of all received comments) voiced support for the pre-NPRM definition of human subject, but expressed support for Alternative A as the least disruptive means of implanting the NPRM.[282]

The second major issue regarding de-identified biospecimens is the NPRM's proposal that research institutions could use broad consent forms to obtain the informed consent to use biospecimens. Many interested parties expressed a concern that this would, in fact, be more injurious to study participants than simply allowing researchers to use de-identified secondary biospecimens.[283] For one, these broad consent documents would be signed prior to the initial research study and many institutions argue that there is no way for an individual to fully consent when it is unclear how those

276. *See* University of Arizona Comment, *supra* note 274 ("The UA opposes the broadening of the definition of "human subjects" to include de-identified biospecimens, except for research with Native Americans or other sovereign groups.").

277. Boston University Comment, *supra* note 229.

278. Stanford University Comment, *supra* note 249; Vanderbilt University Comment, *supra* note 252.

279. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7164 (Jan. 19, 2017) ("The vast majority of commenters who addressed this expansion (80 percent) were opposed to it for a variety of reasons, particularly because of the implications of this change for requiring consent . . . .").

280. *Id.* at 7166.

281. *Id.*

282. *Id.* ("These comments argued that Alternative A would be the least disruptive to the research enterprise, but that the pre-2018 policy would be better.").

283. AAMC Comment, *supra* note 224; Emory University Comment, *supra* note 224; University of California System Comment, *supra* note 224; Vanderbilt University Comment, *supra* note 252.

specimens will be used in the future.[284] These broad consent forms would not stimulate the types of discussion that researchers and participants should be having. Therefore, they are reducing the likelihood that a participant can make a truly informed decision concerning their biospecimens.

Overall, the comments reflect a belief by many interested parties that de-identified biospecimens should remain outside the scope of the Common Rule. Those commenters expressing this opinion also seem to believe that the current definition of human subject is sufficient to provide adequate protection. However, proponents of the expansion, primarily members of the public, argued that it would "respect autonomy by requiring that nearly all research with biospecimens be subject to IRB review and informed consent requirements."[285] Regardless of which side of the argument a particular party falls on, it was clear that HHS needed to clearly delineate whether or not de-identified biospecimens are included in the definition of human subjects in promulgating their final rule.

As a result of the outpouring of opposition to the inclusion of de-identified biospecimens into the definition of human subjects, the Final Rule does not implement this change.[286] HHS, after reviewing the comments, felt that "the public comments on this proposal raise sufficient questions" about the necessity of this addition and that "the current regulatory policy appears to sufficiently protect" secondary biospecimens in research.[287]

As a final note to the concept of de-identified biospecimens, stem cells are another area of human subject research that needs reform.[288] Regardless of the controversy surrounding the harvesting of stem cells, stem cells can provide invaluable insight to a researcher.[289] For stem cell research to be successful, there must be a significant amount of cells.[290] Current regulations provide that federal funding cannot be provided for any research

284. Stanford University Comment, *supra* note 249; University of North Carolina, Comment on the Dept. of Health and Human Services Proposed Rule: Federal Policy for the Protection of Human Subjects (Jan. 5, 2016), http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2015-0008-0602 [https://perma.cc/FM9S-FXAL] [hereinafter University of North Carolina Comment]; Vanderbilt University Comment, *supra* note 252; Yale University Comment, *supra* note 216.

285. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7164.

286. *Id.* at 7168.

287. *Id.*

288. Korobkin, *supra* note 191, at 621–23; Natalie Ram, *Assigning Rights and Protecting Interests: Constructing Ethical and Efficient Legal Rights in Human Tissue Research*, 23 HARV. J.L. & TECH. 119, 175–76 (2009).

289. *Id.* at 137.

290. Korobkin, *supra* note 191, at 609.

that destroys human embryos.[291] Therefore, stem cell research does not currently fall under the Common Rule.[292] The proposed changes to the Common Rule identify neither what protections would be given to stem cells nor if they would be classified as secondary biospecimens.[293] With the growing usage of stem cells in diverse areas of research, at some point in the future, the Common Rule will likely need to address these protections as well.

VI. CONCLUSION

"Medical advances will not reach their full potential if people aren't treated with respect, and informed consent is not granted."[294]

The Common Rule, even prior to the Final Rule, provided numerous invaluable protections to human subjects that choose to participate in research, but case law, history, and ethical controversies show that despite the amazing feats of medical research, terrible things can happen to human subjects in the absence of federal regulations and protections.[295] With the growing use of big data and changes in the research community, the regulations that protect human subjects required change as well.[296] The tragedies of Jesse Gelsinger and Henrietta Lacks occurred under the regulatory framework of the prior Common Rule. HHS took an affirmative step toward providing research participants with the protections they need and deserve by promulgating the Final Rule.[297] These individuals selflessly volunteer their time and bodies. They should be rewarded, at the minimum, with adequate protection and patient autonomy.[298] The Final Rule attempts to promote patient autonomy and remain vigilant in the fast-changing world, while balancing the invaluable need for human subject testing.[299]

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291. *Id.* at 612.

292. *Id.* at 611–12.

293. *See* Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933, 53,936 (Sept. 8, 2015) (failing to mention or address stem cell research).

294. Lacks Family, *supra* note 1.

295. *See supra* notes 96–144 and accompanying text (noting the current regulatory protections afforded to human research subjects under the current Common Rule).

296. Menikoff, *supra* note 156.

297. *See supra* notes 103–12 and accompanying text (discussing the HHS changes to informed consent that will further protect the interests of human research participants).

298. Menikoff, *supra* note 156.

299. *See supra* notes 103–12 and accompanying text (describing how the changes to the informed consent documents will allow patients to make more informed decisions and thus close the gaps within personal autonomy to the participants).

The most significant changes to the Common Rule address a subject's informed consent.[300] The Final Rule makes great strides to increase both transparency of informed consent and the understanding of human research subjects. In requiring the posting of the informed consent document on a government website, research institutions will be held accountable for the informed consent documents they give their subjects.[301] Additionally, disclosing the likelihood of a monetary gain will allow research subjects to make a better-informed decision about whether or not to participate. Provisions such as this one could have made the difference in the life of Jesse Gelsinger or Henrietta Lacks. On that same note, transparency regarding whether the research subject will receive their results back at the completion of the study will open the door for more meaningful dialogue between the researchers and the human subjects. This change may also incentivize greater participation in studies, as many volunteers may choose to participate because they want to better understand a disease or condition. Finally, despite the lack of inclusion of secondary biospecimens in the definition of a human subject, the broad consent document is an available resource for researchers conducting secondary research to utilize in obtaining informed consent. This change promotes subject autonomy while allowing researchers to continue their important research projects. Provisions like this prove that it is possible to maintain a competitive research environment without jeopardizing a patient's right to consent to the study they may participate in.

The Final Rule's changes to the IRB review show a genuine attempt to streamline IRB review and remove unnecessary administrative burdens from human subject research. By removing the mandate for continued review for ongoing research projects that underwent expedited review, IRBs can focus more of their time and resources on high-risk activity. Additionally, by providing a formal list of which activities may qualify for this, IRBs will have a safeguard and will not need to devote time into justifying their decision to forego continued review. This requirement will help create a unified standard for low-risk research projects in all Common Rule agencies. As for the single IRB for cooperative research, the Final Rule will require U.S.-based institutions participating in cooperative research to use a single IRB, but it allows three years before this requirement

300. *See id.* (articulating the new provisions that seek to resolve the current issues in informed consent).

301. *See supra* Part V.A (discussing the requirement to post the informed consent document on a government website).

becomes effective. The last major change to the IRB process is the new exempt categories based on the level of risk associated with the research project. If the risk is minimal, the exempt research would only need to undergo limited IRB review to ensure adequate privacy standards. This, as with many other provisions in the Final Rule, marries the importance of human subject research to the concept of personal autonomy. The efforts of the Final Rule to streamline IRB review, reduce resources allocated to low-risk activity, and to provide ample time for institutions to adjust to these changes all reflect the desire to maintain quality human subject research. As with the informed consent, the Final Rule establishes that personal autonomy can be promoted without jeopardizing valuable research considerations.

The Final Rule fails to adopt the most controversial proposal of the NPRM, the inclusion of secondary biospecimens, regardless of identifiability, into the definition of human subjects. The comments overwhelmingly rejected the proposal from the NPRM to include secondary biospecimens.[302] The comments raised "significant and appropriate concern" for the need for consent of secondary biospecimens.[303] In response to this widespread public opinion, the Final Rule does not subject secondary biospecimens to the Common Rule. This failure to incorporate a new definition does not leave human subjects without recourse in protecting their secondary biospecimens. As stated earlier,[304] under the new informed consent rules, subjects must be informed of any potential research on their secondary biospecimens before agreeing to participate in the project. Further, if a researcher is fully aware of an upcoming project using secondary biospecimens, they can use a broad consent form to obtain the requisite consent from the participant. These safeguards combined with the current regulatory policy are believed to provide adequate protection for a human subject's secondary biospecimens. If nothing else, the discussion created from the NPRM's proposal brought to light important considerations, both academically and ethically, in testing on secondary biospecimens. Whether these provisions will achieve the desired effect of protecting secondary biospecimen can only be determined over time, but, regardless, there is value in the research community conversing over these difficult topics.

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302. *See id.*

303. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7168 (Jan. 19, 2017).

304. *See supra* Part V.A (describing the requirements to disclose any potential research on secondary biospecimens).

Now that the Final Rule has been promulgated, the provisions within the rule will become effective on January 19, 2018.[305] Research institutions and researchers will need to begin preparing now to incorporate the Final Rule in designing future research projects. Until the effective date, the prior Common Rule will remain in regulation. In this fast-paced technology-driven research world, these more clearly articulated protections will hopefully ensure the dignity and autonomy of human research subjects. By considering the comments that interested parties have submitted, HHS has promulgated a Final Rule that allows invaluable human subject research to continue without infringing on the rights of the subjects. These combined considerations will lead to more breakthroughs in medical science and ensure that those who volunteer their bodies for medical science will be adequately protected and safe.

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305. *See* 5 U.S.C. § 553(c) (2012) ("After consideration of the relevant matter presented, the agency shall incorporate in the rules adopted a concise general statement of their basis and purpose.").