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DEPARTMENT OF HOMELAND SECURITY

6 CFR Part 46

DEPARTMENT OF AGRICULTURE

7 CFR Part 1c

DEPARTMENT OF ENERGY

10 CFR Part 745

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

14 CFR Part 1230

DEPARTMENT OF COMMERCE

15 CFR Part 27

SOCIAL SECURITY ADMINISTRATION

20 CFR Part 431

AGENCY FOR INTERNATIONAL DEVELOPMENT

22 CFR Part 225

DEPARTMENT OF JUSTICE

28 CFR Part 46

DEPARTMENT OF LABOR

29 CFR Part 21

DEPARTMENT OF DEFENSE

32 CFR Part 219

DEPARTMENT OF EDUCATION

34 CFR Part 97

DEPARTMENT OF VETERANS AFFAIRS

38 CFR Part 16

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

RIN: 0937-AA02

NATIONAL SCIENCE FOUNDATION

45 CFR Part 690

DEPARTMENT OF TRANSPORTATION

49 CFR Part 11

Federal Policy for the Protection of Human Subjects

AGENCIES: Department of Homeland Security; Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Social Security Administration; Agency for International Development; Department of Justice; Department of Labor; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; and Department of Transportation.

ACTION: Notice of proposed rulemaking.

SUMMARY: The departments and agencies listed in this document propose revisions to modernize, strengthen, and make more effective the Federal Policy for the Protection of Human Subjects that was promulgated as a Common Rule in 1991. 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. This proposed rule is an effort to modernize, simplify, and enhance the current system of oversight. The participating departments and agencies propose these revisions to the human subjects regulations because they believe these changes would strengthen protections for research subjects while facilitating important research.

DATES: To be assured consideration, comments must be received at one of the addresses provided below, no later than 5 p.m. on [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments, identified by docket ID number HHS-OPHS-2015-0008, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov*. Enter the above docket ID number in the "Enter Keyword or ID" field and click on "Search." On the next Web page, click on "Submit a Comment" action and follow the instructions.
- *Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions] to*: Jerry Menikoff, M.D., J.D., OHRP, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.

Comments received, including any personal information, will be posted without change to http://www.regulations.gov.

FOR FURTHER INFORMATION CONTACT: Jerry Menikoff, M.D., J.D., Office for Human Research Protections (OHRP), Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; telephone: 240-453-6900 or 1-866-447-4777; facsimile: 301-402-2071; e- mail: jerry.menikoff@hhs.gov.

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1). NPRM Proposal

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1). NPRM Proposal

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1). NPRM Proposal

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2). Questions for Public Comment

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5). Questions for Public Comment

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a. NPRM Goal

b. Current Rule

c. ANPRM Discussion

d. NPRM Proposal

e. What would change?

f. Questions for Public Comment

3. Waiver of Informed Consent or Documentation of Informed Consent (NPRM at §§__.116(e), (f) and __.117)

a. NPRM Goals

b. Current Rule

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d. NPRM Proposals

e. What would change?

f. Questions for Public Comment

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e. What would change?

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EXECUTIVE SUMMARY

Purpose of the Regulatory Action

Individuals who are the subjects of research may be asked to contribute their time and assume risk to advance the research enterprise, which benefits society at large. U.S. federal regulations governing the protection of human subjects in research have been in existence for more than three decades. The Department of Health, Education, and Welfare (HEW) first published regulations for the protection of human subjects in 1974, and the Department of Health and Human Services (HHS) revised them in the early 1980s. During the 1980s, HHS began a process that eventually led to the adoption of a revised version of the regulations by 15 U.S. federal departments and agencies in 1991. The purpose of this effort was 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 (subpart A of 45 CFR part 46), often referred to as the "Common Rule" for the Protection of Human Subjects.

Since the Common Rule was promulgated, the volume and landscape of research involving human subjects have changed considerably. Research with human subjects has grown in scale and become more diverse. Examples of developments include: an expansion in the number and type of clinical trials, as well as observational studies and cohort studies; a diversification of the types of social and behavioral research being used in human subjects research; increased use of sophisticated analytic techniques for use with human biospecimens; and the growing use of electronic health data and other digital records to enable very large data sets to be analyzed and combined in novel ways. Yet these developments have not been accompanied by major change

in the human subjects research oversight system, which has remained largely unchanged over the last two decades.

The regulations are codified in each department or agency's title or chapter of the Code of Federal Regulations (CFR). The Common Rule was based on HHS' regulations, 45 CFR part 46, subpart A, and includes identical language in the separate regulations of each department and agency.

Although they have not issued the Common Rule in regulations, three departments and agencies currently comply with all subparts of the HHS protection of human subjects regulations at 45 CFR part 46. These are the Central Intelligence Agency (CIA), the Department of Homeland Security (DHS), and the Social Security Administration (SSA). DHS, and SSA are joining this proposed rulemaking with the intent of codifying the final rule in their own agency regulations.

Pursuant to Executive Order 12333 of December 4, 1981, as amended, elements of the Intelligence Community must comply with the guidelines issued by the Department of Health and Human Services regarding research on human subjects found in 45 CFR Part 46. This proposed rulemaking does not supersede the Executive Order. The Office of the Director of National Intelligence and the CIA will continue to adhere to the HHS guidelines, pursuant to the Executive Order, when the final rule is implemented.

DHS, created after issuance of the Common Rule, is required by statute (Pub. L. 108-458, title VIII, section 8306) to comply with 45 CFR part 46, or with equivalent regulations promulgated by the Secretary of Homeland Security or his designee. This proposed rulemaking initiates the

process of promulgating equivalent regulations, consistent with statute. Once DHS executes a final rule, DHS will comply with the DHS regulations as the requirements will be equivalent to compliance with HHS regulations at 45 CFR part 46, subpart A.

SSA was separated from HHS in 1995 and, pursuant to the transition rules provided in Section 106 of title 1 of Pub.L. 103-296, must apply all regulations that applied to SSA before the separation, absent action by the Commissioner. Once the final rule is codified in SSA regulations, SSA will follow the SSA regulations instead of HHS regulations at 45 CFR part 46, subpart A. See Pub. L. 103-296 § 106(b), 108 Stat. 1464, 1476.

Another department is joining this proposed rulemaking. The Department of Labor (DOL) is not a signatory to the current Common Rule, and is joining this proposed rulemaking in order to promulgate the Common Rule in DOL regulations and to apply the regulations to human subjects research that DOL may conduct or support, pending the scope of the final rule.

Finally, note that there are two current Common Rule agencies that are not listed as part of this proposed rulemaking. The Department of Housing and Urban Development (HUD) supports this proposal, but due to certain statutory prepublication requirements governing HUD rules, HUD will adopt this proposal through a separate rulemaking. The Consumer Product Safety Commission (CPSC), subject to Commission vote, also intends to adopt this proposed rule through a separate rulemaking.

On July 26, 2011, the Office of the Secretary of HHS, in coordination with the Executive Office of the President's Office of Science and Technology Policy (OSTP), published an advanced

notice of public rulemaking (ANPRM) to request comment on how current regulations for protecting human subjects who participate in research might be modernized and revised to be more effective.[1] The ANPRM sought comment on how to better protect human subjects who are involved in research while facilitating valuable research and reducing burden, delay, and ambiguity for investigators.

Since the publication of the ANPRM, science has continued to advance, as has the dialogue regarding the changing nature of research and the preferred balance of protections for research participants among the principles of respect for persons, beneficence, and justice. Important elements of that debate have centered on the appropriate level of transparency in government and medicine and how patient and research participant expectations should be incorporated into government policies. These factors have helped shape the development of the regulatory actions proposed in this NPRM.

The proposal also benefits from public comments submitted in response to more recent policy proposals regarding specific topics such as informed consent through the Office for Human Research Protection (OHRP)'s Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care[2] and the use of a single institutional review board (IRB) for multi-site research studies through the National Institutes of Health (NIH)'s Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research.[3]

[1] 76 FR 44512 (Jul. 26, 2011).
[2] 79 FR 63630 (Oct. 24, 2014).
[3] National Institutes of Health. (2014, December 14). Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. See more at: http://grants.nih.gov/grants/guide/notice-

Finally, the NPRM more thoroughly addresses behavioral and social science research perspectives and the broader types of research conducted or otherwise supported by the other Common Rule agencies. Similarly, the proposal benefits from continuing efforts at HHS to harmonize human subjects policies, particularly between OHRP and the U.S. Food and Drug Administration (FDA).

Summary of the Major Provisions of the Proposed Regulatory Action

The goals of the NPRM are to increase human subjects' ability and opportunity to make informed decisions; reduce potential for harm and increase justice by increasing the uniformity of human subject protections in areas such as information disclosure risk, coverage of clinical trials, and coverage of IRBs; and facilitate current and evolving types of research that offer promising approaches to treating and preventing medical and societal problems through reduced ambiguity in interpretation of the regulations, increased efficiencies in the performance of the review system, and reduced burdens on researchers that do not appear to provide commensurate protections to human subjects. It is hoped that these changes will also build public trust in the research system.

An example of some major changes being proposed that will better protect research subjects and help build public trust are the rules relating to informed consent. With regard to informed consent in general (such as consent to participating in clinical trials), the rules would be

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files/NOT-OD-15-026.html#sthash.fmjlNRi6.dpuf. Retrieved from National Institutes of Health, Office of Extramural Research: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html

significantly tightened to make sure that the process becomes more meaningful. Consent forms would no longer be able to be unduly long documents, with the most important information often buried and hard to find. They would need to give appropriate details about the research that is most relevant to a person's decision to participate in the study, such as information a reasonable person would want to know, and present that information in a way that highlights the key information. In addition, to assure that these rules do indeed change current practices, there will be a one-time posting requirement for the consent forms for clinical trials, so that anyone drafting a consent form will do so knowing that it will eventually be subject to public scrutiny.

In addition, informed consent would generally be required for secondary research with a biospecimen (for example, part of a blood sample that is left over after being drawn for clinical purposes), even if the investigator is not being given information that would enable him or her to identify whose biospecimen it is. Such consent would not need to be obtained for each specific research use of the biospecimen, but rather could be obtained using a "broad" consent form in which a person would give consent to future unspecified research uses.

The NPRM also attempts to strengthen the effectiveness and efficiency of the oversight system by making the level of review more proportional to the seriousness of the harm or danger to be avoided. Research that poses greater risk to subjects should receive more oversight and deliberation than less risky research. The NPRM seeks to avoid requirements that do not enhance protection and impose burden, which can decrease efficiency, waste resources, erode trust, and obscure the true ethical challenges that require careful deliberation and stakeholder input. Cumbersome and outdated regulatory standards overwhelm and distract institutions, IRBs, and

investigators in ways that stymie efforts to appropriately address the real risks and benefits of research.

The result of these types of changes, as the NPRM proposes to implement them, is that some studies that currently require IRB review would now become exempt. Some that are currently exempt would specifically be declared as outside the scope of the regulations ("excluded"), and thus would not require any administrative or IRB review. Further, in terms of determining when a study is exempt, a web-based "decision tool" will be created. That decision tool will provide a determination of whether or not a study is exempt. That result, so long as the tool was provided with accurate information, will be presumed by the Common Rule agencies to be an appropriate determination of exempt status. Thus, it is expected that in many instances the tool would be used by the investigators themselves, thus obviating both the need for further review and the concern that the institution might be subjecting itself to future liability by allowing investigators to use the tool. For all of the excluded and exempt research activities, this NPRM also affirms the importance of applying the ethical principle of respect for persons, in addition to the importance of abiding by this principle in fully regulated non-exempt research involving human subjects.

The following list encompasses the most significant changes to the Common Rule proposed in the NPRM:

1) Improve informed consent by increasing transparency and by imposing stricter new requirements regarding the information that must be given to prospective subjects, and the

manner in which it is given to them, to better assure that subjects are appropriately informed before they decide to enroll in a research study.

2) Generally require informed consent for the use of stored biospecimens in secondary research (for example, part of a blood sample that is left over after being drawn for clinical purposes), even if the investigator is not being given information that would enable him or her to identify whose biospecimen it is. That consent would generally be obtained by means of broad consent (i.e., consent for future, unspecified research studies) to the storage and eventual research use of biospecimens.

3) Exclude from coverage under the Common Rule certain categories of activities that should be deemed not to be research, are inherently low risk, or where protections similar to those usually provided by IRB review are separately mandated.

4) Add additional categories of exempt research to accommodate changes in the scientific landscape and to better calibrate the level of review to the level of risk involved in the research. A new process would allow studies to be determined to be exempt without requiring any administrative or IRB review. Certain exempt and all non-exempt research would be required to provide privacy safeguards for biospecimens and identifiable private information. New categories include:

a. certain research involving benign interventions with adult subjects;

b. research involving educational tests, surveys, interviews or observations of public behavior when sensitive information may be collected, provided that data security and information privacy protections policies are followed;

c. secondary research use of identifiable private information originally collected as part of a non-research activity, where notice of such possible use was given;

d. storing or maintaining biospecimens and identifiable private information for future, unspecified secondary research studies, or conducting such studies, when a broad consent template to be promulgated by the Secretary of HHS is used, information and biospecimen privacy safeguards are followed, and limited IRB approval of the consent process used is obtained.

5) Change the conditions and requirements for waiver or alteration of consent such that waiver of consent for research involving biospecimens (regardless of identifiability) will occur only in very rare circumstances.

6) Mandate that U.S. institutions engaged in cooperative research rely on a single IRB for that portion of the research that takes place within the United States, with certain exceptions. To encourage the use of IRBs that are otherwise not affiliated with or operated by an assurance-holding institution ("unaffiliated IRBs"), this NPRM also includes a proposal that would hold such IRBs directly responsible for compliance with the Common Rule.

7) Eliminate the continuing review requirement for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing data or involve only observational follow-up in conjunction with standard clinical care.

8) Extend the scope of the policy to cover all clinical trials, regardless of funding source, conducted at a U.S. institution that receives federal funding for non-exempt human subjects research.

In sum, the proposed modifications described above are designed to continue to uphold the ethical principles upon which the Common Rule is based, as applied to the current social, cultural, and technological environment.

The legal authority for the departments and agencies that are signatories to this action is as follows:

Department of Homeland Security, 5 U.S.C. 301; P.L. 107-296, sec. 102, 306(c); P.L. 108-458, sec. 8306. Department of Agriculture, 5 U.S.C. 301. Department of Energy, 5 U.S.C. 301; 42 U.S.C. 7254. National Aeronautics and Space Administration, 5 U.S.C. 301. Department of Commerce, 5 U.S.C. 301. Social Security Administration, 5 U.S.C. 301; 42 U.S.C. 289(a). Agency for International Development, 5 U.S.C. 301. Department of Justice, 5 U.S.C. 301; 28 U.S.C. 509-510. Department of Labor, 5 U.S.C. 301; 29 U.S.C. 551. Department of Defense, 5 U.S.C. 301. Department of Education, 5 U.S.C. 301; 20 U.S.C. 1221e-3, 3474. Department of Veterans Affairs, 5 U.S.C. 301; 38 U.S.C. 501, 7331, 7334. Environmental Protection Agency, 5

U.S.C. 301. Department of Health and Human Services, 5 U.S.C. 301; 42 U.S.C. 289. National Science Foundation, 5 U.S.C. 301. Department of Transportation, 5 U.S.C. 301.

Estimated Costs and Benefits

Table 1 summarizes the quantified and non-quantified benefits and costs of all proposed changes to the Common Rule. Over the 2016-2025 period, present value benefits of $2,629 million and annualized benefits of $308 million are estimated using a 3 percent discount rate; present value benefits of $2,047 million and annualized benefits of $291 million are estimated using a 7 percent discount rate. Present value costs of $13,342 million and annualized costs of $1,564 million are estimated using a 3 percent discount rate; present value costs of $9,605 million and annualized costs of $1,367 million are estimated using a 7 percent discount rate. Non-quantified benefits include improved human subjects protections in clinical trials and biospecimen research not currently subject to oversight; enhanced oversight of research reviewed by unaffiliated IRBs; increased uniformity in regulatory requirements among Common Rule agencies; standardization of human subjects protections when variation among review IRBs is not warranted; revised informed consent forms and processes; improved protection of biospecimens and individually identifiable private information; and increased transparency of Common Rule agency-supported clinical trials to inform the development of new consent forms. Non-quantified costs include the time needed for consultation among Common Rule agencies before federal guidance is issued; and the time needed by investigators to obtain, document, and track the permissible uses of biospecimens and identifiable private information for secondary research use.

Table 1. Accounting Table of Benefits and Costs of All Proposed Changes

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits	2,629	2,047	308	291
Non-quantified Benefits Improved human subjects protections in clinical trials and biospecimen research not currently subject to oversight; enhanced oversight in research reviewed by unaffiliated IRBs; increased uniformity in regulatory requirements among Common Rule agencies; ethical benefit of respecting an individual's wishes in how his or her biospecimens are used in future research; standardization of human subjects protections when variation among review IRBs is not warranted; improved informed consent forms and processes; improved protection of biospecimens and individually identifiable private information; better ensuring availability of biospecimens for future research activities; and increased transparency of Common Rule-supported clinical trials to inform the development of new consent forms.				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs	13,342	9,605	1,564	1,367
Non-quantified Costs Time for consultation among Common Rule agencies before federal guidance is issued; time for investigators to obtain consent for secondary use of biospecimens or identifiable private information.				

I. The Rationale for Modernizing the Common Rule

A. The Changing Nature of Research

In the last two decades there has been a paradigm shift in how research is conducted. Evolving technologies, including imaging, mobile technologies, and the growth in computing power have

changed the scale of information collected in many disciplines. Computer scientists, engineers, and social scientists are developing techniques to integrate different types of data so they can be combined, mined, analyzed, and shared. Research has also increased, evolved, and diversified in other areas, such as national security, crime and crime prevention, economics, education, and the environment, using a wide array of methodologies in the social sciences and multidisciplinary fields. The advent of sophisticated computer software programs, the internet, and mobile technology has created new areas of research activity, particularly within the social and behavioral sciences. In biomedical science, the Human Genome Project laid the foundation for precision medicine and promoted an environment of data sharing and innovation in analytics and technology, and drew attention to the need for policies that support a changing research landscape. New technologies, including genomic sequencing, have quickly led to exponential growth in the data to which investigators have access. The sheer volume of data that can be generated in research, the ease with which it can be shared, and the ways in which it can be used to identify individuals were simply not possible, or even imaginable, when the Common Rule was first adopted.

Research settings are also shifting. While much biomedical research continues to be conducted in academic medical centers, more research is being conducted in clinical care settings, thus combining research and medical data. Biospecimen repositories and large databases have made it easier to do research on existing biospecimens and data. Clinical research networks connected through electronic health records (EHRs) have developed methods for extracting clinical data for research purposes and are working toward integration of research data into EHRs in a meaningful way. The overall volume of research has increased across the board, with growing

reliance on research networks and multi-site studies. Large cohort studies number well into the hundreds in the United States alone and many collect biospecimens and data on the same people over many years. Recent trends clearly show that the scientific community recognizes the value of data sharing and open-source resources and understands that pooling intellectual resources and capitalizing on efficient uses of data and technology represent the best ways to advance knowledge.

At the same time, the level of public engagement in the research enterprise has changed; more people want to play an active role in research, particularly related to health, and they have different expectations than when the Common Rule was first established. A more participatory research model is emerging in social, behavioral, and biomedical research, one in which potential research subjects and communities express their views about the value and acceptability of research studies. This participatory model has emerged alongside a broader trend in American society, facilitated by the widespread use of social media, in which Americans are increasingly sharing identifiable personal information and expect to be involved in decisions about how to further share the personal information, including health-related information that they have voluntarily chosen to provide. In many ways, these changes are extensions of the fact that over the past half-century, rather than being passive recipients of health advice and treatment, patients have gradually become more active in decisions about their health and health care. The shift from a paternalistic research environment to one where participants are active partners in biomedical and behavioral research is a critical development in human subjects research.

As technology evolves, so does the nature of the risks and benefits of participating in certain types of research. Many studies do not involve interaction with research subjects, but instead involve, for example, analyzing information obtained from medical records, administrative claims data, education records, criminal justice records, research data shared through data repositories, and existing biospecimens stored in repositories. Risks related to these types of research studies are largely informational, not physical; that is, harms could result primarily from the inappropriate release of information and not from the research interventions themselves. Nonetheless, those harms can be significant.

New methods, more powerful computers, and easy access to large administrative datasets produced by local, state, and federal governments have meant that some types of data that formerly were treated as non-identified can now be re-identified through combining large amounts of information from multiple sources. In 2013, scientists demonstrated that the identity of individual research subjects could be ascertained by collating and analyzing certain types of genomic data, including genomic data from publicly available information sources.[4] Thus, the possibility of fully identifying biospecimens and some types of data from which direct identifiers had been stripped or did not originally include direct identifiers has grown, requiring vigilance to ensure that such research be subject to appropriate oversight. Most importantly, people want to be asked for their permission. A growing body of survey data show that many prospective

[4] Gymrek M et al. "Identifying personal genomes by surname inference". *Science* 339.6117(2013) 0: 321-324.

participants want to be asked for their consent before their biospecimens are used in research.[5,6,7,8]

Because of these shifts in science, technology, and public engagement expectations, a wide range of stakeholders have raised concerns about the limitations of the existing framework, arguing for a re-evaluation of how the fundamental principles that underlie the Common Rule —respect for persons, beneficence, and justice—are applied in practice to the myriad new contexts in which U.S. research is conducted in the 21st century.[9,10] Dialogue focuses around whether the current system:

- is sufficiently supportive of a participant-centered research model that adequately respects participants as partners;
- is not sufficiently risk-based, resulting in both over- and under-regulation of research activities;[11,12,13]

[5] Kaufman DJ et al. Public opinion about the importance of privacy in biobank research. *American Journal of Human Genetics* 2009 Nov;85(5):643-654.
[6] Vermeulen E et al. A trial of consent procedures for future research with clinically derived biological samples. *British Journal of Cancer* 2009 Nov 3;101(9):1505-1512.
[7] Trinidad SB et al. Research practice and participant preferences: The growing gulf. *Science* 2011 Jan 21; 331(6015):287-288.
[8] Simon CM et al. Active choice but not too active: Public perspectives on biobank consent models. *Genetics in Medicine*. 2011 Sep;13(9):821-831.
[9] Emanuel EJ, Wood A, Fleischman A, et al. Oversight of human participants research: Identifying problems to evaluate reform proposals. *Annals of Internal Medicine* 2004;141(4):282-291.
[10] Maschke K. Human research protections: time for regulatory reform? *Hastings Center Report*. 2008 Mar-Apr; 38(2):19-22.
[11] Kim S, Ubel P, De Vries R. Pruning the regulatory tree. *Nature* 2009 Jan 29;457(7229):534-535.
[12] Wendler D, Varma S. Minimal risk in pediatric research. *Journal of Pediatrics*. 2006 Dec;149(6):855-861.
[13] Infectious Disease Society of America. Grinding to a halt: The effects of the increasing regulatory burden on research and quality improvement efforts. *Clinical Infectious Diseases* 2009 Aug 1;49(3):328-335.

- is sufficiently tailored to new and emerging areas of research, including social and behavioral research and research involving the collection and use of genetic information;[14,15,16,17,18,19]
- effectively informs subjects of psychological, informational, or privacy risks;[20,21,22]
- adequately accounts for the needs of a "learning" healthcare system for continual quality improvement;[23,24,25]
- provides sufficient mechanisms to ensure the consistency, quality, and accountability of IRB decision-making.[26,27,28,29]

B. Public Comments, Expert Advice, Stakeholder Dialogue

[14] National Research Council. *Protecting Participants and Facilitating Social and Behavioral Sciences Research*. Washington DC: National Academies Press, 2003.
[15] Anderlik M. Commercial biobanks and genetic research: ethical and legal issues. *American Journal of Pharmacogenomics* 2003;3(3):203-215.
[16] Schrag ZM. How talking became human subjects research: The Federal regulation of the social sciences, 1965–1991. *Journal of Policy History* 2009 January; 21(01):3-37.
[17] Hansson MG et al. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncology* 2006 Mar; 7(3):266-269.
[18] Murphy J et al. Public perspectives on informed consent for biobanking. *American Journal of Public Health* 2009 December; 99(12):2128-2134.
[19] Kaufman DJ et al. Public opinion about the importance of privacy in biobank research. *American Journal of Human Genetics* 2009 Nov; 85(5):643-654.
[20] Paasche-Orlow MK, Taylor HA, Brancati F. Readability standards for informed-consent forms as compared with actual readability. *New England Journal of Medicine* 2003 Feb 20; 348(8):721-726.
[21] Schneider CE. The Hydra. *Hastings Center Report* 2010 Jul-Aug; 40(4):9-11.
[22] Albala I, Doyle M, Appelbaum PS. The evolution of consent forms for research: A quarter century of changes. *IRB Ethics & Human Research* 2010 May-June; 32(3):7-11.
[23] Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. *New England Journal of Medicine* 2014 Feb 20;370(8):766-768.
[24] Dziak K et al. Variations among institutional review board reviews in a multisite health services research study. *Health Services Research* 2005 Feb; 40(1):279-290.
[25] Lynn J et al. The ethics of using quality improvement methods in health care. *Annals of Internal Medicine* 2007 May 1;146(9):666-673.
[26] Heimer CA et al. Regulating creativity: Research and survival in the IRB iron cage. *Northwestern University Law Review* 2007; 101:593-641.
[27] Green LA et al. Impact of institutional review board practice variation on observational health services research. *Health Services Research* 2006 Feb; 41(1):214-230.
[28] Jansen LA. Local IRBs, multicenter trials, and the ethics of internal amendments. *IRB* 2005 Jul-Aug;27(4):7-11.
[29] Schrag Z. *Ethical Imperialism*. Baltimore, MD: Johns Hopkins University Press, 2010.

The revisions to the Common Rule proposed here are based upon a variety of sources of public, stakeholder, and expert comments and advice. First, the NPRM more thoroughly addresses social science and behavioral research perspectives, benefiting from guidance provided by a National Research Council's consensus report entitled "Proposed Revisions to the Common Rule for the Protection of Human Subjects in the Behavioral and Social Sciences."[30] The Report was commissioned to ensure that the issues related to research involving human subjects in social and behavioral research would be addressed appropriately, in view of what had been said in the ANPRM. The Panel made numerous recommendations, including recommendations about what research studies should not undergo review, about calibrating the level of IRB review to the level of risk, about the desirability of privacy and confidentiality protections in social and behavioral research other than those of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and about improving informed consent by placing greater emphasis on the process of consent. The NPRM revises some of the ANPRM proposals in light of those recommendations.

Second, since the publication of the ANPRM, HHS has continued to solicit public comment on a variety of human subjects related issues, including consent, the use of a single IRB for multi-site studies, and sharing of genomic data. Although these policies were more specific than the issues raised in the ANPRM, the responses received from public comments provide insight for refining the proposals initially put forward in the ANPRM. Of particular interest:

[30] National Research Council of the National Academies. (2014). Proposes Revisions to the Common Rule for the Protections of Human Subjects in the Behavioral and Social Science. The National Academies Press, 13-168. Retrieved from http://www.nap.edu/catalog/18614/proposed-revisions-to-the-common-rule-for-the-protection-of-human-subjects-in-the-behavioral-and-social-sciences

- NIH's proposal that it expects the use of a single IRB for all multi-site research studies funded or conducted by the NIH.[31] Under that proposal, all domestic sites of a multi-site study would be expected, as a condition of NIH funding, to use a single IRB of record. In response to this proposal, NIH received 165 comments from a range of stakeholders, including investigators, IRB members, and members of the public. The majority of respondents were supportive; however concerns were raised that it would be expensive and time-consuming to identify a single IRB for each new multi-site study.
- OHRP's draft guidance discussing the required content of consent language for research done within the standard of care.[32] In August of 2013, prior to the publication of the draft guidance document, HHS held a public meeting to hear from the community on issues raised during the debate surrounding the SUPPORT study.[33] The public meeting and the draft guidance document spurred a significant public discussion about the nature of the information included in informed consent forms, specifically how investigators should communicate the risks of research studies done within the standard of care. A total of 93 comments were received from bioethicists, investigators and research institutions, hospitals and physicians, IRB members, patient advocates, and industry.
- To enhance human subject protections and reduce regulatory burden, OHRP and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research, and the FDA's draft guidance, "Use of Electronic Informed Consent in Clinical Investigations" was developed as part of these efforts. The

[31] National Institutes of Health. (2014, December 14). Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. See more at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html#sthash.fmjlNRi6.dpuf. Retrieved from National Institutes of Health, Office of Extramural Research: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html
[32] 79 FR 63630 (Oct. 24, 2014).
[33] 78 FR 48163 (Aug 7, 2013).

draft guidance was issued in conjunction with an OHRP Federal Register notice soliciting comment on the whether joint final guidance would be useful for the regulated community, and whether FDA's draft guidance would be appropriate for all research regulated under 45 CFR part 46, such as social and behavioral research studies. Comments were received largely favoring joint guidance, but with separate sections addressing research regulated solely by 45 CFR part 46.

- NIH's proposal to promote sharing of large-scale human genomic data generated from studies funded or conducted by NIH.[34] The policy lays out an expectation that investigators generating genomic data get consent for future research use of those data. The NIH received 107 comments on the policy, including many that addressed the concept of broad consent for unspecified future research use.

There have also been developments on the legislative front that have informed the discussions leading up to this NPRM. In December of 2014, the Newborn Screening Saves Lives Reauthorization Act of 2014 (Pub. L. 113-240), was signed into law. The new law makes a number of changes relevant to the HHS regulations for protecting research subjects, including declaring that research with newborn dried blood spots that is federally funded pursuant to the Public Health Service Act is to be considered research with human subjects, and the provisions allowing IRBs to waive consent will not apply. These changes will be effective until updates to the Common Rule are promulgated. In addition, in April of 2015, the Medicare Access and CHIP Reauthorization Act of 2015 (Pub. L. 114-10) was passed. That law requires HHS to issue a

[34] 79 FR 51345 (Aug. 28, 2014).

clarification or modification of the Common Rule with regard to how they apply to activities involving clinical data registries.

Most recently, with the launch of the President's Precision Medicine Initiative (PMI)[35,36], the Federal Government is proposing a new research cohort based on a model that puts participants at the center.[37] To understand participant preferences the White House and PMI agencies have been hosting a series of roundtables and public workshops about public expectations for how participants want to engage in research today. These discussions have included individuals from many sectors, including prospective research participants, patients and patient advocates, privacy experts, bioethicists, academic and industry investigators, data scientists, technology innovators, healthcare institutions and providers. The government has heard many perspectives, with much alignment around the central tenet that participants should be active partners in research, and not merely passive subjects of research studies. Many are seeking a research environment where they can contribute to the greater good and have transparency into the research being conducted using their specimens and data. The conversations have focused on promoting the ethical principles of respect for persons, beneficence, and justice, as well as promoting other protections, such as data security and privacy.

C. Guiding Principles for Proposed Changes

[35] The White House, Office of the Press Secretary. (2015, January 30). Fact Sheets: President Obama's Precision Medicine Initiative. Retrieved from The White House: https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

[36] Collins FS, Varmus H. A New Initiative on Precision Medicine. *N Engl J Med* 2015 Feb; 372:793-795.

[37] See also http://www.scientificamerican.com/article/big-precision-medicine-plan-raises-patient-privacy-concerns/, http://www.nih.gov/precisionmedicine/, and http://www.nih.gov/precisionmedicine/.

In 1979, the Belmont Report[38] was predicated on three principles that were felt to be central to shaping an ethical framework for the conduct of research with human subjects. The three ethical principles are respect for persons, beneficence, and justice. Interpretation of, and balancing among, these three principles played a major role in shaping what became the development the federal regulations that have become known as the Common Rule. The preamble to the proposal considers whether and how the interpretation of these fundamental principles might be updated within the context of the current technological, social, cultural, and ethical environment. That consideration involves explicitly identifying the interplay among the principles. The Common Rule provides a framework for how researchers and IRBs weigh the often conflicting implications of these three principles.

Beneficence: Individuals who participate in research contribute their time and may assume significant risks to advance the research enterprise. Their valuable contributions produce knowledge that benefits society at large. The Belmont Report describes the principle of beneficence as the goal of maximizing possible benefits of research and minimizing possible harms. This principle has been interpreted to, in part, emphasize the benefit associated with the knowledge that might be generated by a research study. Evaluating beneficence requires examining the likelihood that knowledge would be generated, and how important or useful that knowledge might be to the population. When more weight is given to research that has the potential to generate a great deal of knowledge, particularly knowledge that could be very useful

[38] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). Belmont Report. Washington, D.C.: U.S. Department of Health & Human Services. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.

to society (such as how to treat serious diseases that are currently untreatable), policies would lean in favor of encouraging and facilitating more of that type of research.

A distinct aspect of the principle of beneficence concerns the benefits and risks to the specific persons who would be participating in a particular research study. In the example of a randomized clinical trial comparing two treatments for a disease, the benefits and risks to the subjects in the trial are distinct from the possible benefits to society as a whole from learning which of the two treatments is better. This aspect of beneficence assumes that there are limits on the risks to which people should be subject, even if they are willing to undergo those risks.

Society is in an information age. In all facets of one's life information about that person is generated, stored, shared, analyzed, and often provides tremendous societal value. People share information about themselves with large numbers of people with the click of a button, and this trend of rapid and widespread sharing is only likely to grow. The increase in concern about unauthorized and inadvertent information disclosure, in combination with newer research techniques that increase the volume and nature of identifiable data suggest the need for the Common Rule to more explicitly address data security and privacy protection.

Of particular interest for this proposal is addressing risks from inappropriate disclosure of information generated from biospecimens. One way to protect subjects from such risks is to bring under oversight research for which risks are greater of subjects being identified and information being inappropriately disclosed. Although it may be difficult to identify individuals from their non-identified biospecimens at present, and most investigators would have no need to

do so unless they were seeking additional associated phenotypic information, certain technologies and methods can be used to generate data that are unique to the individual who provides the biospecimen, and those data can sometimes be combined with other data sources to identify the individual. In the future, technologies will facilitate the use and analysis of greater variety and volumes of information, and there is a possibility that it will be increasingly difficult, if not impossible, to make biospecimens fully non-identified. In fact, a number of reports have already demonstrated the ability to re-identify individuals from biospecimens or data that lack direct identifiers.[39,40] As analytic techniques become more sophisticated and large datasets become more accessible, it will not be possible to guarantee that an individual could never be identified from a biospecimen or combination or data sources, particularly if whole genome sequencing is conducted.

Respect for Persons: The Belmont Report describes this concept as the notion of treating people as autonomous agents, and allowing them to make choices based on their own judgments and opinions. Inherent in the principle of autonomy is the concept of transparency— clearly providing the information necessary for the research participant to make such judgments. Transparency requires a clear articulation of risks, potential benefits, and alternatives to participating in a research study, as well as the purpose of the research. The principle of autonomy encompasses the value ascribed to an individual's right to know how one's data is being used and who will have access to it. As such autonomy also covers the paired concept of

[39] Rothstein MA. Is deidentification sufficient to protect health privacy in research? *American Journal of Bioethics* Sep 2010; 10(9): 3–11.
[40] El Emam K et al. A systematic review of re-identification attacks on health data. *PLoS One* 2011; 6(12):e28071.

protecting those persons who lack the capability to make such decisions. There are a variety of different ways of demonstrating respect for persons.

Obtaining informed consent from human subjects for the collection and analysis of information about them is one means of implementation of respect for persons in the research context. Informed consent is designed to ensure that each individual approached to participate in a research study fully understands the risks and potential benefits of the study so that they have sufficient information to make an individualized calculation as to whether or not the tradeoffs inherent in participation are worth it for them to agree to participate. Both the potential harms and benefits tend to be greater in the context of a clinical trial where subjects are randomized to one or another of two possible treatments with significantly different suspected risks than in situations where subjects are simply asked to provide, for instance, a urine sample.

Notice, in which individuals are informed about how data will be used, but explicit consent is not obtained, is another means of facilitating transparency. Notice is sometimes used in the context of informing people about how data collected for non-research purposes (e.g., when providing information in the context of applying for public benefits) might be used for either general or specific research purposes. Another method for showing respect for persons with regard to using data about them for research could be providing them with a right to opt out of such research, by, for example, filing a form stating such a wish with the holder of the data.

Related, implicit consent might be obtained when a research subject completes a questionnaire. If they did not wish to provide the information, presumably they would not be answering the

questions. The NPRM contains a number of provisions that are designed to further promote respect for participants through increases in both transparency and opportunities for consent.

Justice: The Belmont Report describes this principle as being about fairness in terms of who receives the benefits from research and who bears its burdens. One of the most direct applications of the principle of justice to the Common Rule relates to determining who is studied and how subjects are selected. This principle also is relevant to protection of vulnerable populations. In addition, the idea of justice is relevant to one of core goals of this NPRM: clarifying important aspects of the Common Rule where there has been ambiguity in interpretation. To the extent that IRBs and others interpret the regulations in significantly different ways, the result is that participants in research can end up being treated in very different ways, even when they are participating in the same study. Thus this idea is embedded in all of the NPRM's attempts to make sure that these rules are applied in a more uniform and consistent manner.

The three ethical principles of the Belmont Report often cannot all be fulfilled at the same time. In many cases, it will be necessary to choose which of those principles will deserve the greatest adherence. This NPRM, at its heart, represents an attempt to evaluate the weights to be applied to each of these three core principles in a variety of specific contexts. Giving greater weight to one of the principles will frequently mean a decreased ability to fulfill one of the other principles. By necessity, value judgments, influenced by the social norms of the time, drive the implementation of the broad principles underlying the Belmont Report. The efficacy of the oversight system also requires proportionality in weighing the application of these three principles. This is reflected in

the analysis that follows, in terms of evaluating the specific aspects of beneficence, respect for persons, and justice that relate to a particular issue, and weighing those aspects against one another. Research that poses greater risk should receive more attention and deliberation than less risky research, and the degree and type of oversight should be commensurate with the level of risk. In addition, requirements that do not enhance protection but that impose burden can increase inefficiency, waste resources, erode trust, and obscure the ethical challenges that require careful deliberation and stakeholder input. Cumbersome and outdated regulatory standards overwhelm and distract oversight bodies and other stakeholders from appropriately addressing the real risks and benefits of research.

There is tremendous support for research in this country. American society values advances in knowledge and has reaped the reward of many key insights that have led to increases in quality of life and a doubling of our life expectancy in the last century. There would not have been such strides in medical and behavioral research without the willingness of individuals to join research studies. Participants are told that they are not likely to benefit directly from any given study, yet they choose to participate for the greater good. Beneficence is a powerful driver. On the other hand, members of the public deserve, and indeed now expect, to know how publicly-funded research is being conducted and overseen, and need to have confidence that the interests of research participants are adequately protected. Transparency is key for developing trust, especially between investigators, funders, regulators, and the public.

Our reassessment of these ethical principles in the context of current technology and social norms suggests the need for changes to the Common Rule that: (1) increase subject autonomy by

increasing human subjects' ability and opportunity to make informed decisions; (2) reduce potential for harm and increase justice by increasing the uniformity of human subject protections in areas such as information disclosure risk, coverage of clinical trials, and coverage of IRBs; and (3) increase beneficence by facilitating current and evolving types of research that offer promising approaches to treating and preventing medical and societal problems though reduced ambiguity in interpretation of the regulations, increased efficiencies in the performance of the review system, and reduced burdens on researchers that do not appear to provide commensurate protections to human subjects. If a reasonable balance is struck between protecting human research subjects, minimizing the administrative burden of the system, and engendering public trust, this should maximize beneficence and raise all ships.

Public comment is sought not only on the provisions outlined below, but on whether the proposals strike a reasonable balance among the core ethical principles. A better balance among the core principles should increase the strength of the partnership between the research enterprise and the public, and even greater scientific understanding and innovation will be fostered.

Finally, it is important to note that, to the extent appropriate, the intent is to eventually amend the other subparts of the HHS human subjects protection regulations in 45 CFR part 46 (subparts B, C, D, and E), and consider the need for updates to FDA regulations and other relevant Federal departmental or agency regulations with overlapping scope.

1. Question for Public Comment

1. Public comment is sought on whether the proposed changes will achieve the objectives of (i) decreasing administrative burden, delay and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects.

D. Organization of the NPRM

Section II of the NPRM, which immediately follows, describes in detail the major proposals for revisions to the Common Rule. In general, the changes that are likely to be of greatest significance are discussed in the earlier parts of section II of this preamble. Section II.A is devoted to changes that affect which activities are subject to the Common Rule. Following that section are discussions devoted to changes relating to informed consent (section II.B), changes relating to privacy safeguards for the research use of information and biospecimens (section II.C), and a proposal to encourage greater harmonization of guidance across the agencies that adhere to the Common Rule (section II.D). Discussions of changes relating to how IRBs operate, including a proposal to reduce the number of reviews by different IRBs that take place for multi-site studies, are in the several sections that follow (sections II.E, F and G). The final section (section II.H) collects a variety of other changes, including expanding the scope of the rule to cover clinical trials that are not federally funded but are conducted at institutions that received some federal funding for research with human subjects.

The three sections that follow then discuss various administrative review requirements: Regulatory Impact Analyses (section III), Environmental Impact (section IV), and Paperwork

Reduction Act (section V). The final section of the document (section VII) provides the full regulatory text of the proposed changes to the Common Rule. Section VI provides a comprehensive summary of responses received to the 2011 Common Rule ANPRM.

II. Major Proposals to Modernize the Common Rule

A. Proposed Changes to the Scope and Applicability of the Regulations

1. Expanding the Definition of Human Subject to Cover Research with Non-identified Biospecimens (NPRM at §§__.102(e) and __.101(b)(3)(i))

This section focuses on the ethical principles associated with the secondary research use of biospecimens. These biospecimens may have been originally collected from either research or non-research settings (e.g., leftover portion of tissue from a clinical biopsy).

a. NPRM Goals

One of the goals of this NPRM is facilitating cutting edge research in genomics and other 'omics' such as the transcriptome and the microbiome, which generate a wealth of data from biospecimens designed to inform the development of treatments and preventative measures for chronic diseases such as cancer. Facilitating such research, however, requires navigating complex ethical issues. The key question is, under what circumstances should the Common Rule govern what research investigators are able to do with biospecimens that have been collected for

some other (e.g., clinical) purpose? (Note that if a researcher interacted with an individual to actually collect a biospecimen for research purposes—for example, obtaining a saliva sample—that "primary" research activity is already covered under the current regulations, and is not the focus of the change discussed in this section.) In this case, maximizing the societal value of research would mean reducing barriers to the secondary use of biospecimens to the extent possible.

However, there is a growing recognition that many people want to have some degree of control over the circumstances in which an investigator can derive information about them, above and apart from their interest in whether or not that information might be inappropriately disclosed. More specifically, a growing body of literature shows that in general people prefer to have the opportunity to consent (or refuse to consent) to research involving their own biological materials.[41] Furthermore, in 2012, the Presidential Commission for the Study of Bioethical Issues highlighted the ethical importance of obtaining consent for genomics research and recommended that "unauthorized whole genome sequencing without the consent of the individual from whom the sample came" be prohibited.[42] Their rationale for reaching this conclusion was based on concerns relating to privacy as well as autonomy.

In assigning weights to the principles of beneficence and respect for persons in the context of research with biospecimens, strong consideration was given to the fact that failure to acknowledge and give appropriate weight to this distinct autonomy interest in research using

[41] *See supra* notes 5-8.
[42] Presidential Commission for the Study of Bioethical Issues. (2012). Privacy and Progress in Whole Genome Sequencing. Washington,D.C.: Presidential Commission for the Study of Bioethical Issues. Retrieved from http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf.

biospecimens could, in the end, diminish public support for such research, and ultimately jeopardize our ability to be able to conduct the appropriate amount of future research with biospecimens. To that end, the proposals given below are designed to meet the goals of increasing transparency in when and how biospecimens collected in a variety of circumstances will be used for research purposes and increasing opportunities for consent. Various ways in which these goals might be achieved are the subject of alternative proposals discussed below.

b. Current Rule

The application of the current regulations to secondary research use of a biospecimen is tied to the identifiability of the biospecimen in the hands of the researcher. In particular, the definition of human subject in the current Common Rule at §__.102(f) states that a human subject is a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. Private information is described as information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Consistent with historical interpretation of identifiable private information under the Common Rule, the terms "non-identified" or "non-identifiable" are used throughout this NPRM to signify biospecimens or data that have been stripped of identifiers such that an investigator cannot readily ascertain a human subject's identity. Re-identification of non-identified or non-

identifiable biospecimens or information may be possible, depending on the circumstances. The term "de-identified" is distinct; it is only used in this proposal to refer specifically to the HIPAA standard of non-identifiability.

Thus, where there is no intervention or interaction with an individual, central to determining whether human subjects are involved in a research activity covered by the current Common Rule is determining the meaning of "identifiable." Under the current Rule, provided the biospecimens and data were collected for purposes other than the currently proposed research, it is permissible for investigators to conduct research on biospecimens and data that have been stripped of all identifiers without obtaining consent because the non-identified biospecimens and data do not meet the regulatory definition of human subject.

It is, however, worth noting that although informed consent is not strictly required by the current regulations when research takes place using non-identified biospecimens, some IRBs have indicated that they are requiring that investigators explicitly obtain consent for future analysis of biospecimens collected in the research setting, and some are refusing to waive consent for use of biospecimens collected in non-research contexts.

c. ANPRM Discussion

The ANPRM asked whether consent should be required before an investigator could conduct research on a non-identified biospecimen. It further asked, if consent were to be required, could such consent be obtained by having a person provide consent for unspecified future research with

the biospecimen, instead of requiring that specific consent be obtained each time that the biospecimen would actually be used in a research study.

Although HHS does not consider whole genome analysis to produce identifiable private information unless additional information is available to the investigator that would enable the investigator to "readily ascertain" the identity of the individual, it is acknowledged that a time when investigators will be able readily ascertain the identity of individuals from their genetic information may not be far away. The ANPRM suggested that, regardless of what information is removed, it is theoretically possible to extract DNA from a biospecimen itself and potentially link it to otherwise available data to identify individuals. In addition, irrespective of whether biospecimens are considered individually identifiable, the ANPRM sought comment on whether the regulations should be changed to allow human subjects to decide whether their biospecimens would be available for research.

The ANPRM asked whether some types of genomic data should be considered identifiable and, if so, which types (e.g., genome-wide single nucleotide polymorphism [SNP] analyses or whole genome sequences). It also asked whether a human biospecimen should be considered inherently identifiable.

The ANPRM also suggested that the definition of identifiability in the Common Rule be modified to better harmonize it with other regulatory definitions of identifiability within HHS. The ANPRM considered adopting the HIPAA Privacy Rule's standards of what constitutes individually identifiable information, a limited data set, and de-identified information (as defined

under HIPAA), in order to address inconsistencies regarding these definitions and concepts between the HIPAA Privacy Rule and the Common Rule.

More specifically, as described above, private information is not considered to be identifiable under the current Rule if the identity of the subject is not or may not be "readily ascertained" by the investigator from the information or associated with the information. In contrast, under the HIPAA Privacy Rule, health information is de-identified and thus exempt from that rule only if it neither identifies nor provides a reasonable basis to believe that the information can be used to identify an individual. The HIPAA Privacy Rule provides two ways to de-identify information: (1) a formal determination by a qualified expert that the risk is very small that an individual could be identified; or (2) the removal of all 18 specified identifiers of the individual and of the individual's relatives, household members, and employers, as long as the covered entity has no actual knowledge that the remaining information could be used to identify the individual (45 CFR 164.514(b)).

The HIPAA Privacy Rule addresses some informational risks by imposing restrictions on how individually identifiable health information collected by health plans, health care clearinghouses, and most health care providers ("covered entities") may be used and disclosed, including for research. In addition, the HIPAA Security Rule (45 CFR Parts 160 and, subparts A and C of part 164) requires that these entities implement certain administrative, physical, and technical safeguards to protect this information, when in electronic form, from unauthorized use or disclosure. However, the HIPAA Rules apply only to covered entities (and in certain situations to their business associates), and thus not all investigators are part of a covered entity and required

to comply with those rules. Moreover, the HIPAA Rules do not apply specifically to biospecimens in and of themselves.

Public comments in response to the 2011 ANPRM regarding covering all biospecimens raised a series of important concerns. A majority of the commenters opposed the ANPRM's suggested requirement of consent for research use of all biospecimens, regardless of identifiability, particularly if applied to samples collected before the effective date of the regulation. Some commenters cited lack of convincing evidence of harm caused by research use of non-identified clinical biospecimens without consent; they noted that they were not convinced that the principle of autonomy outweighs or trumps the principle of beneficence. They expressed concern that doing so would significantly slow advances in research and human health.

Others acknowledged the erosion of public trust that can result from high-profile disputes involving the use of non-identified biospecimens collected during research.[43] Commenters cited the costs to collect, log, and track consent status of data and biospecimens collected in a clinical setting to ensure that any restrictions on the research use of such resources were honored. However, it is important to note that it appears that many commenters were reacting to concerns that any change in the Common Rule with respect to consent for use of biospecimens would be applied retroactively—that is, to samples already collected.

Some patient advocacy organizations also expressed concerns about the consequences of requiring consent for the use of non-identified biospecimens. Other commenters noted that the

[43] National Congress of American Indians. Havasupai Tribe and the lawsuit settlement aftermath. Retrieved on November 17, 2014, from http://genetics.ncai.org/case-study/havasupai-Tribe.cfm.

recommendation to require consent might inappropriately give greater weight to the Belmont Report's principle of autonomy over the principle of justice, because requiring consent could result in lower participation rates in research by minority groups and marginalized members of society. Yet, most of the comments from individual members of the public strongly supported consent requirements for use of their biospecimens, regardless of identifiability.

Many commenters expressed the opinion that the existing regulatory framework is adequate and that current practices should be maintained, stressing that the research use of non-identified data or biospecimens does not involve risk to the research participant. Furthermore, several commenters noted that, although it is theoretically plausible to identify a person based on their biospecimen, the likelihood remains remote enough to argue against the presumption that the sources of all biospecimens are identifiable and cited a study showing that the risk of re-identification from a system intrusion of databases was only 0.22%.[44] In contrast, some commenters supported the idea of requiring consent for research use of all biospecimens, with one commenter noting simply that "research use of data initially collected for non-research purposes should always require informed consent."

Several commenters stated that if the Common Rule were modified such that all biospecimens were covered under the rule regardless of identifiability there still might be some activities involving biospecimens that should be considered exempt or excluded from coverage. Suggestions included:

[44] Kwok P et al. Harder Than You Think: A Case Study of Re-Identification Risk of HIPAA-Compliant Records. NORC at The University of Chicago and Office of the National Coordinator for Health Information Technology. 2011. http://www.amstat.org/meetings/jsm/2011/onlineprogram/AbstractDetails.cfm?abstractid=302255

- Identifying markers for cancer prognosis or prediction of response to cancer therapy, or identifying cancer molecular targets (molecular research)
- Basic science research (including analysis of biological processes)
- Research on rare conditions and diseases
- Pediatric research
- Research with samples that lack potentially identifying information, such as serum or plasma not containing DNA
- Biospecimens lacking nucleic acids (such as certain red blood cells, expiratory gases)
- Blood culture bacteria
- Bacterial and viral specimens (this was listed in a comment as a public health issue)
- Protein analysis
- Statistical method development (to the extent that this development is related to biospecimens)
- New molecular methods to detect infectious agents
- Use of specimens to develop and validate new assays for infectious agents
- Archival paraffin blocks

With respect to the 2011 proposal to adopt the HIPAA Privacy Rule's definition of identifiability, a majority of the public commenters strongly opposed the idea. They indicated that the HIPAA Privacy Rule's standard of identifiability would expand what is considered identifiable for purposes of the Common Rule and thus greatly impede relatively low-risk research without adding meaningful protections for human subjects. In particular, they asserted

that the HIPAA standards were created to protect against disclosure of health information contained in medical records. As such, commenters argued, they are not appropriate for many types of research that would be covered by the Common Rule (e.g., behavioral and social science research). Others said this would be an extreme change in response to an as yet unidentified or clear problem. Commenters said that the information most at risk for inappropriate disclosure is the type of private health information that is already protected under the HIPAA Rules. Commenters feared that such a change in policy, while "harmonizing" the Common Rule to certain HIPAA standards, would create inordinate burdens in terms of new documentation requirements and result in a requirement to apply the HIPAA standards to all types of research, regardless of the level of risk.

d. NPRM Proposal

Regardless of the scale on which harms may have occurred in the past, continuing to allow secondary research with biospecimens collected without consent for research places the publicly-funded research enterprise in an increasingly untenable position because it is not consistent with the majority of the public's wishes, which reflect legitimate autonomy interests. As such, one of the most fundamental changes proposed in this NPRM is to the definition of human subject (proposed §__.102(e)). The proposal is for the obtaining, use, study, or analysis of biospecimens to be covered under the Common Rule, regardless of identifiability. Covering biospecimens regardless of identifiability avoids codifying any given interpretation of the quickly evolving debates regarding whether certain analytic results (e.g., decoding the whole genome) should be considered to yield identifiable data. (Accompanying this proposal are some minor wording

changes to other portions of that definition that are merely intended to clarify how the word "obtains" is currently interpreted by OHRP.)

Thus, the focus of this proposal is to require informed consent for research involving biospecimens in all but a limited number of circumstances. The consent would not need to be obtained for each specific study using the biospecimen, but could instead be obtained through broad consent for future unspecified research (described in more detail in sections II.A.3.d and II.B of this preamble).

An increase in trust and partnership is likely to increase participation rates in research; using individuals' samples and data without permission will hinder true partnership. Better communication and community engagement with patients, particularly in geographic areas and for population subgroups where consent rates are lower than average, should be a priority for the research community.

In response to comments received about the 2011 ANPRM, the NPRM proposes to have the new definition of human subject apply prospectively, that is, it will only apply to research involving biospecimens that will be collected in the future. Additionally, in recognizing that this proposal will have major implications for the operational functioning of the research enterprise, compliance with this provision would be delayed until three years after publication of a final rule.

Also consistent with comments received on the ANPRM, it is proposed that a subset of secondary research on stored biospecimens would be allowed without consent. Specifically, research designed to only generate information about the person that is already known would be considered outside of the scope of the Common Rule. This exclusion would include but not be limited to the development and validation of certain tests and assays (such as research to develop a diagnostic test for a condition using specimens from individuals known to have the condition and those known not to have the condition), quality assurance and control activities, and proficiency testing. This provision would be implemented through a new exclusion from the regulations at §__.101(b)(3)(i), which has specifically been designed to reflect the underlying ethical principles.

If the research is designed not to generate any new information about the person, but only confirm something about them that is already known, then the interest in respecting the person's autonomy would appear to be relatively weak. As an example, imagine that a person is known to have a particular genetic disease, and the research involves evaluating a new product that might in a few minutes, at low cost, produce a result showing whether a person has that disease. The person's autonomy interest in whether or not such a study could take place would seem little different from that of anyone in a study that involved secondary use of identifiable information about them.

In addition, the proposal permits IRBs to waive the requirement for informed consent, but the requirements for approval of such waivers would be very strict, and such waivers will only occur in rare circumstances. Note also that the exclusions proposed in §__.101(b)(1)(i), (iii)-(vi) would

also allow for the use of biospecimens without consent in certain limited circumstances; these additional exclusions are discussed in section II.A.2 of this preamble, below.

This proposal would not modify the Common Rule standard of identifiability (in contrast to what was discussed in the 2011 ANPRM). That is, the standard for determining when an investigator has sufficient information to readily ascertain the identity of an individual is not being changed under this proposal. Thus, coverage of information derived from biospecimens (whether or not the biospecimen was initially collected in the research or non-research context), or indeed any other type of information, would be the same under this proposal as is the case under the current Common Rule.

i. Alternative Proposals

In this section, we discuss two alternative proposals, both of which maintain "identifiability" as the lynchpin for determining applicability of the Common Rule to biospecimens. These models increase transparency and opportunities for consent over and above what is provided for in the current Common Rule, but in a smaller set of circumstances than provided for under the primary proposal discussed above.

Alternative Proposal A: Expand the Definition of "Human Subject" to Include Whole Genome Sequencing (WGS)

Rather than consider all research using biospecimens as constituting human subjects research, this alternative proposal would expand the definition of human subjects to include only specifically whole genome sequencing data, or any part of the data generated as a consequence of whole genome sequencing, regardless of the individual identifiability of biospecimens used to generate such data. Under this alternative, whole genome sequencing would be considered the sequencing of a human germline or somatic biospecimen with the intent to generate the genome or exome sequence of that biospecimen.

Thus, under this alternative, the regulations would then apply both to research that would generate whole genome sequencing data, the use of any part of the generated data, and to research involving secondary use of any part of whole genome sequencing data that was originally generated for other purposes than the proposed research. Investigators conducting whole genome sequencing research could not avoid the need to comply with the Common Rule by removing identifiers from biospecimens or data, because whole genome sequence data in and of itself would meet the definition of human subject. Under this alternative, a new exemption would also be created that would allow such research to be considered exempt if consent to secondary future research use were obtained in accordance with proposed new requirements at §__.116(c) and standards were met for protecting information and biospecimens as proposed at §___.105. A waiver of consent would be permitted, but would be modeled on the more stringent waiver criteria proposed for research involving biospecimens at §__.116(f)(2).

Explicit consent to conduct research using whole genome sequencing data can be considered ethically important because such data can provide important insights into the health of

individuals as well as their relatives. Moreover, whole genome sequence data gathered for one purpose may reveal important information, perhaps unanticipated and unplanned for, years later. Finally, whole genome sequence data are unique for each individual, or at the very least, highly unlikely to be the same as any other individual. Thus, the current allowable practice of removing identifiers from biospecimens and data to conduct whole genome sequencing research without consent might not sufficiently protect both the privacy and autonomy interests of the subject.

As is currently the case, under this alternative, investigators' use of individually identifiable biospecimens, collected for purposes other than the currently proposed research study, would continue to be considered human subjects research. However, the secondary research use of non-identified information or non-identified biospecimens would continue to fall outside of the scope of the Common Rule, with the exception of whole genome sequence data as described above.

One of the less obvious differences in scope between the primary proposal and this Alternative A relates to what research could be done with the data generated from whole genome sequencing that had taken place for clinical purposes. Under the primary proposal, the data produced by such sequencing could continue to be used for research, without additional consent, so long as it did not meet the definition of being identifiable private information. (HHS does not currently consider whole genome sequencing data to meet that definition for purposes of the Common Rule.) Under this Alternative A, consent would be required before using that data for research purposes.

In contrast with the primary proposal in this NPRM, this Alternative Proposal A could be viewed as giving greater weight to the principle of beneficence, while giving less weight to the principle of respecting the autonomy of persons. It would require consent only for the type of studies that many people seem most concerned about (genomic research, including secondary use of genomic information that was produced for clinical purposes). And given that at the moment there is relatively little whole genome sequencing research taking place (in comparison to other types of biospecimen research; see section III.F of this preamble for more information), it would appear to currently impose a somewhat lesser burden in terms of obtaining and tracking consent than the main NPRM proposal.

The major concern with this alternative proposal is that it would codify only a single technology as producing information that would be subject to the Common Rule, necessitating a re-evaluation of the scope of the Rule when technologies now in development to study, for instance, other "omics," become more widespread.

Alternative Proposal B: Classifying Certain Biospecimens Used in Particular Technologies as Meeting the Criteria for "Human Subject"

This Alternative Proposal B would expand the definition of human subjects to include the research use of information that was produced using a technology applied to a biospecimen that generates information unique to an individual such that it is foreseeable that, when used in combination with publicly available information, the individual could be identified. Information that met this standard would be referred to as bio-unique information. This proposal is

conceptually very similar to Alternative Proposal A. The main difference is that the scope is somewhat broader: whereas Alternative A requires consent for whole genome sequencing, Alternative B would require consent for genomic sequencing of even small portions of a person's genome, and also require consent for the use of other technologies that might be developed that similarly can generate information unique to a person.

There are three separate conditions that would all need to be met before information would constitute bio-unique information: (1) It would have to have been produced by applying to a biospecimen a technology that is capable of producing information that is unique to an individual; (2) The technology would have to be used to produce enough information such that the information produced is likely to be unique to an individual; and (3) There would need to be publicly available information that, when combined with the information produced by the use of the technology, would create the possibility that some of the individuals whose biospecimens were analyzed using the technologies could be identified.

The major concern with this alternative proposal is that, in order to make such a requirement responsive to scientific and technological developments, HHS would have to continually evaluate new technologies and the nature and amount of information produced using such technologies. Not only would this involve resources and expertise that may not be available to Federal departments and agencies, it would introduce ongoing uncertainty that may actually increase delays in important research.

e. What Would Change in the Definition Of "Human Subject" under the Primary Proposal?

- It is anticipated that the compliance date for the proposed expansion of the definition would be three years after the publication date. The main consequence of this change would be that informed consent (which could be broad, as described in sections II.A.3.d and II.B of this preamble) would generally be required before research use of biospecimens not covered by an exclusion.
- All biospecimens used for research purposes that do not fall under an exclusion (see proposed §__.101(b)(3)(i), and also §__.101(b)(1)(i), (iii)-(vi)) and are collected after the compliance date would be subject to the requirements of this rule, regardless of identifiability.

f. Questions for Public Comment

2. Would providing a definition of biospecimen be helpful in implementing this provision? If so, how might the definition draw a line between when a biospecimen is covered by the Common Rule, and when processing of biological materials (e.g., to create a commercial product used for treatment purposes) has sufficiently altered the materials so that they should not be subject to the regulations? Would only covering biospecimens that include nucleic acids draw an appropriate line?

3. To what extent do the issues raised in this discussion suggest the need to be clearer and more direct about the definition of identifiable private information? How useful and appropriate is the current modifier "may be readily ascertained" in the context of modern genomic technology, widespread data sharing, and high speed computing? One alternative is to replace the term "identifiable private information" with the term used across the Federal Government: personally identifiable information (PII). The Office of Management and Budget's[45] concept of PII refers to information that can be used to distinguish or trace an individual's identity (such as their name, social security number, biometric records, etc.) alone, or when combined with other personal or identifying information which is linked or linkable to a specific individual, such as date and place of birth, mother's maiden name, etc. It is acknowledged that replacing "identifiable private information" with "PII" would increase the scope of what is subject to the Common Rule. However, the practical implications of such an expansion, other than the need to ensure that the data are security stored and otherwise protected against disclosure, may be minimal. Public comment is requested on the advantages and disadvantages of such a change.

4. Which of the three proposals regarding the definition of human subject achieves the most reasonable tradeoff between the principles of autonomy (including transparency and level of trust) versus beneficence (as measured by facilitating valuable research)?

5. Public comment is sought regarding any concerns that you have about each of the three proposals, including concerns about implementation or burden to investigators and institutions.

[45] Executive Office of the President, Office of Management and Budget. (2007). Memorandum for the Heads of Executive Departments and Agencies. Retrieved from The White House: https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2007/m07-16.pdf

2. Explicit Exclusion of Activities from the Common Rule

The NPRM creates a new section in the regulations referred to as "exclusions." This section outlines eleven specific types of activities that will be outside the scope of the regulations. These activities will therefore not have to satisfy any regulatory requirements, nor is it expected (unlike exempt research) that they will undergo any type of review process to determine this status. The exclusions will eliminate uncertainty regarding some activities that are not research, and identify some activities that arguably might be judged to be research, but whose contribution to public welfare is so imperative that they should proceed without having to satisfy the regulatory requirements. The exclusions also identify certain research activities that are sufficiently low-risk and nonintrusive that the protections provided by the regulations are an unnecessary use of time and resources, whereas the potential benefits of the research are substantial.

The Common Rule has been criticized for not being clear about how to interpret what activities are covered by the policy and for inappropriately being applied to and inhibiting certain activities. The first six exclusion categories are for activities that are deemed not to be research for the purposes of this policy, without needing to consider whether the regulatory definition applies. The definition of research does not provide such a clear and precise way of distinguishing among similar activities that it is immediately obvious which activities fall under the definition and which do not. By creating exclusion categories that are deemed not research, these activities are more clearly distinguished as not having to satisfy the regulatory requirements.

Three of the exclusions seek to eliminate any uncertainty about whether certain internal program improvement activities, historical or journalistic inquiries, or quality assurance or improvement activities satisfy the definition of research. The other three exclusions include some activities that fall into to a gray area that encompasses some activities that arguably might be judged to be research, but that are part of inherently governmental functions that have purposes other than research, such as responsibilities to protect public health and welfare (see exclusions for criminal investigations, public healthy surveillance, and intelligence surveillance). These activities promote recognized specific goods that are crucial to the public welfare, and should be carried out without any hindrances that satisfying regulatory requirements might impose. For these activities, the principles of beneficence and justice outweigh any intrusions on individual autonomy that the regulations might have prevented.

The next four categories of proposed exclusions are for activities that are considered low-risk either in themselves or because there are appropriate safeguards already in place independent of the Common Rule. Here the level of risk, the potential benefits, and the nature of human participation in this research are such that the principle of beneficence determines that the research activities may go forward without the need to impose the protections of the Common Rule.

The last exclusion applies to research involving the secondary use of non-identified biospecimens when the research is limited to generating information about the subject that is already known. As such, this research does not need any additional protections provided by

these regulations and the potential benefits of this research justify it under the principle of beneficence. Because this exclusion directly relates to the proposed changes in the definition of "human subject" to include all biospecimens, it is discussed above in section II.A.1 of this preamble.

It should be noted that the fact that the NPRM now specifically includes a list of certain excluded activities should not be seen as altering the fact that many other activities that do not meet the criteria for being subject to the Common Rule remain outside the scope of the rule. For example, an activity that does not meet the regulatory definition of research, or does not involve human subjects, would still not be subject to these regulations.

Currently, the Common Rule excludes from coverage (1) activities that do not meet the definition of research (§__.102(d) of the current Rule); (2) activities that are not described as research subject to regulation (§__.102(e) of the current Rule); and (3) activities that do not involve a human subject (§__.102(f) of the current Rule).

The ANPRM asked questions about the definition of research and whether various activities should be excluded from the Common Rule, either by changing the definition of research or by adding exemptions, or both. The ANPRM sought comment on whether and, if so, how, the Common Rule should be changed to clarify whether quality improvement activities, program evaluation studies, or public health activities are covered. It also asked whether there are specific types of studies for which the existing rules are inappropriate. If so, comments were sought on whether this problem should be addressed through modifications to the exemption categories, or

by changing the definition of "research" used in the Common Rule to exclude some of these studies, or a combination of both.

If the definition of research were to be changed, public comment was sought on how excluded activities should be defined (e.g., "quality improvement" or "program evaluation"). With regard to quality improvement activities, the public was asked to comment on whether it might be useful to adopt the distinction made by the HIPAA Privacy Rule, which distinguishes between "health care operations" and "research" activities, defining "health care operations" to include, among other activities, "conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities."

a. Exclusion of Activities that are Deemed Not Research (NPRM at §___.101(b)(1))

The first set of six exclusions involve activities that will be excluded from the regulations because they will be deemed to not involve research. Three of the first six exclusions (discussed in sections II.A.1.a.i, ii, and iv, below) provide clarity regarding the applicability of the Common Rule to activities about which institutions have raised questions in the past as to whether these activities meet the regulatory definition of research. These exclusions aim to reduce the time and effort involved trying to determine whether the regulations apply, and in unnecessary reviews of these activities.

The other three of these exclusions (discussed in sections II.A.1.iii, v, and vi below) apply to activities that are largely inherently government functions that have purposes other than research, and, when conducted by a government employee or contractor, are subject to a variety of other statutes, regulations, and polices that are designed to protect individual privacy and data security, as well as provide notice to those providing the information as to the uses to which the information will be put (see, for example, the Privacy Act of 1974). These activities promote recognized specific goods that are crucial to the public welfare, and because of this they should be carried out without any hindrances that satisfying the Common Rule regulatory requirements might impose. For these activities, the principle of beneficence outweighs any intrusions on individual autonomy that the regulations might have prevented, and this allows these important activities to proceed without delay.

The ANPRM asked whether various activities such as quality improvement, public health activities, or program evaluations studies should be excluded from the rule.

i. Program Improvement Activities (NPRM at §___.101(b)(1)(i))

1). NPRM Proposal

The first exclusion, proposed in the NPRM at §__.101(b)(1)(i), is for data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purpose other than the currently

proposed activity, or is obtained through oral or written communications with individuals (e.g., surveys or interviews). This category is excluded because these activities are designed for various administrative purposes related to using information to improve the quality of services provided by a specific institution, and are not designed to produce generalizable knowledge. A majority of commenters to the 2011 ANPRM supported excluding program evaluation activities from the scope of the Common Rule. Many of these commenters argued that the public benefits resulting from this type of activity justified its practice, particularly given the generally low-risk involved.

An example of an activity that would satisfy this exclusion is a survey of hospital patients to evaluate and improve the quality of meals delivered to hospital patients. An example of an activity that would not satisfy this exclusion is a prospective observational study of patient treatments to analyze the comparative effectiveness of two different standard of care treatments frequently used to treat the same medical condition.

2). Questions for Public Comment

6. Public comment is sought for whether this excluded activity should simply be discussed in the text of the final rule's preamble, and guidance produced to assist investigators in making such a determination, or whether any other similar exclusions should be addressed.

7. Public comment is sought for whether biospecimens should not be included in any of these exclusion categories, and if so, which ones.

ii. Oral History, Journalism, Biography, and Historical Scholarship Activities (NPRM at §___.101(b)(1)(ii))

1). ANPRM Discussion

The ANPRM asked whether there were any fields of study (such as classics, history, languages, literature, and journalism) whose usual methods of inquiry were not intended to or should not be covered by the Common Rule.

2). NPRM Proposal

The second proposed exclusion, in the NPRM at §__.101(b)(1)(ii) is for oral history, journalism, biography and historical scholarship activities that focus directly on the specific individuals about whom the information is collected.

The overwhelming majority of public comments to the 2011 ANPRM responding to the question about excluding specific fields of study from the regulatory requirements of the Common Rule supported explicitly excluding certain activities from the definition of research versus modifying the exemption categories. The overwhelming majority of these comments focused on oral history. Some of the comments were virtually identical and appear to have been coordinated. Many of the comments reflected the view that the Common Rule was not designed or intended to

include oral history activities, and that the ethical codes pertaining to oral history procedures are not consistent with the application of the ethical principles reflected in the Common Rule.

A smaller number of similar comments were submitted with respect to various humanities disciplines and journalism. A significant minority of commenters opposed the exclusion of any fields of study, arguing that the activity itself rather than the academic discipline or training of the investigator should be the basis for the assessment of whether the activity should be excluded. Some of the commenters recommended that the definition of research be focused more explicitly by being limited to "biomedical and behavioral research," in accordance with the statutory provision underlying the Common Rule. A significant number of commenters recommended that guidance should be issued to clarify how the definition of research should be applied, with cases and explanations.

While the NPRM does not propose to modify the definition of "research", it does propose to explicitly exclude oral history, journalism, biography, and historical scholarship activities that focus directly on the specific individuals about whom the information or biospecimens is collected. In the kinds of activities referred to here, the ethical requirement is to provide an accurate and evidence-based portrayal of the individuals involved, and not to protect them from public scrutiny. Therefore, the protections afforded to individuals by the Common Rule seem unhelpful in furthering the aforementioned ethical goal in this context. Additionally, these fields of research have their own codes of ethics, according to which, for example, consent is obtained for oral histories. It is believed that because of these reasons, explicit exclusion of these activities from the scope of the Common Rule is appropriate.

iii. Criminal Justice Activities (NPRM at §___.101(b)(1)(iii))

1). NPRM Proposal

The third category of activities that the NPRM excludes from the proposed rule encompasses data collection and analysis that enables the uniform delivery of criminal justice. The scope of this exclusion is collection and analysis of data, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. The activities excluded are necessary for the operation and implementation of the criminal justice system.

The provision would essentially codify current Federal interpretation that such activities are not deemed to be research under the Common Rule. The addition of this provision is designed to avoid the imposition of disparate requirements by IRBs with overlapping jurisdiction when a data collection or analysis activity encompasses the development of methods required by law or court order for criminal justice or criminal investigative purposes. For example, the Federal Bureau of Investigation (FBI) is charged by law with setting standards governing the collection and processing of DNA biospecimens and information taken (forcibly if necessary) from certain federal and state criminal offenders incident to their arrest or conviction for prescribed offenses under the National DNA Identification Act of 1994 and other acts. Similarly, the FBI is charged by law with setting standards governing the collection and processing of fingerprints and related biographical information taken from federal and state criminal offenders and certain sensitive

civil employment applicants. At the same time, through its Laboratory Division and other components the FBI routinely collects human biospecimens at crime scenes from or relating to victims and offenders both known and unknown. Incident to these activities, the FBI is also charged with maintaining, and authenticating through identification processes, the criminal record history information of criminal offenders for the Federal Government and for the overwhelming majority of state governments who elect to participate and share information through those FBI systems.

iv. Quality Assurance and Quality Improvement Activities (NPRM at §___.101(b)(1)(iv))

1). NPRM Proposal

The fourth category of excluded activities covers quality assurance or improvement activities involving the implementation of an accepted practice to improve the delivery or quality of care or services (including, but not limited to, education, training, and changing procedures related to care or services) if the purposes are limited to altering the utilization of the accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. This exclusion does not cover the evaluation of an accepted practice itself.

As an example of an activity that would satisfy this exclusion, assume that there is an accepted practice that is known to reduce the likelihood of an infection after the insertion of a central line. A randomized study in which half the participating institutions would be assigned to have the staff undergo an educational intervention about the need to use that accepted practice, and the

other half would not undergo that intervention, would satisfy this exclusion, since it would only be intended to see if the intervention resulted in greater use of the accepted practice. In contrast, imagine a different study that was designed to determine how well that accepted practice, when it is used, reduces infections. That study would not satisfy this exclusion, since it would be studying the effectiveness of the practice itself, in contrast to studying an effort to increase use of the practice.

Over the past several years, including in response to the 2011 ANPRM, OHRP has received comments from many individuals and organizations expressing concern that some readings of the definition of "research" would imply that the regulations apply to quality improvement activities, thereby potentially interfering with the ability of health care and other professionals to enhance the delivery or quality of care or services involving the use of accepted practices. Indeed, a majority of commenters to the 2011 ANPRM supported excluding quality improvement activities from the scope of the Common Rule. These quality improvement activities are in many instances conducted by health care and other organizations under clear legal authority to change internal operating procedures to increase safety or otherwise improve performance, often without the consent of staff or clients, followed by monitoring or evaluation of the effects. These activities are generally conducted in circumstances where independent privacy, confidentiality, and security safeguards are in place, minimizing the chances of harm. These efforts, some of which could be judged to be research, should be carried out because of the recognized public good they achieve. This exclusion is intended to avoid impeding such efforts where the Common Rule's requirements might have a chilling effect on the ability to learn from, and conduct, important types of innovation.

Recognizing that some quality improvement efforts should not be considered to involve research as it is defined in the Common Rule can allay many of these concerns. Thus, this exclusion is being proposed to deal with quality improvement activities that are aimed at implementing practices that are already accepted, with the goal of improving the delivery or quality of treatments or services. This exclusion would permit measuring and reporting provider performance data for practice management, clinical, or administrative uses. As proposed, this exclusion does not include evaluations of different accepted practices themselves, however, such as activities designed to determine whether a particular accepted medical treatment is or is not more effective than another.

This provision also covers quality improvement activities that are not related to delivery of patient care, but rather involve the delivery or quality of other public benefit or social services. For example, institutions and other entities may provide social services, educational offerings, or other beneficial activities where there is empirical evidence of the value of those efforts, and they may wish to evaluate different ways of enhancing the delivery or quality of those existing services. This exclusion has been written broadly to include such activities.

The rationale for this excluded category is that these activities are designed only to improve the implementation of a practice that is already accepted, not to evaluate the effectiveness and value of the accepted practice itself, and thus would generally be expected to pose little if any risks to the recipients of those practices, and are directly aimed at improving the practical use of those practices. This does not include quality improvement activities designed with a research purpose

relating to the safety and efficacy of the accepted practice. It is accordingly important to note that activities that do involve such research—for example, assigning patients to different versions of treatments that are within the standard of care in order to evaluate the differences between those treatments in terms of effectiveness or risks—would not come within this exclusion. In the educational context, for example, activities where students are assigned to experimental and control groups to determine the effectiveness of experimental teaching methodologies would also not come within this exclusion. Furthermore, that type of activity would also not meet a separate requirement of this exclusion—that the activity be related to the delivery of (i.e., implementing) an accepted form of care, and not an attempt to evaluate the efficacy or risks of that form of care.

v. Public Health Surveillance (NPRM at §___.101(b)(1)(v))

1). NPRM Proposal

The fifth category of excluded activities involves public health surveillance activities, including the collection and testing of biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority and limited to those necessary to allow the public health authority to identify, monitor, assess, or investigate potential public health signals or the onset of a disease outbreak, including trends, or signals, and patterns in diseases, or sudden increase in injuries from using a consumer product, or conditions of public health importance, from data, and including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made

disasters. A majority of commenters to the 2011 ANPRM supported excluding public health activities from the scope of the Common Rule.

The rationale for excluding some public health surveillance activities is that when a public health authority conducts public health surveillance activities to fulfill its legal mandate to protect and maintain the health and welfare of the populations it oversees, the regulatory protections of the Common Rule should not impede its ability to accomplish its mandated mission of promoting this recognized public good, in keeping with the principle of beneficence. Other protections independent of the Common Rule exist that serve to protect the rights and welfare of individuals participating in such activities, including privacy, confidentiality and security safeguards for the information collected.

Public health surveillance refers to the collection, analysis, and use of data to target public health prevention. It is the foundation of public health practice. Surveillance uses data from a variety of sources, including mandatory reporting of certain conditions, routine monitoring, vital records, medical billing records, and public health investigations in response to reports of potential outbreaks. The line between public health surveillance and epidemiological research can be difficult to draw, as the same techniques may be used in both. Generally, the difference between the activities is the purpose or context in which the investigation is being conducted and the role of the public health authority.

The following are examples of activities that meet the public health surveillance exclusion:

- Safety and injury surveillance activities designed to enable a public health authority to identify, monitor, assess, and investigate potential safety signals for a specific product or class of products (for example, the surveillance activities of the FDA's Adverse Event Reporting System (AERS), the Vaccine Adverse Event Reporting System (VAERS), Manufacturer and User Facility Device Experience (MAUDE) database, the Medical Product Safety Network (MedSun), and the Sentinel Initiative);
- Surveillance activities designed to enable a public health authority to identify unexpected changes in the incidence or prevalence of a certain disease in a defined geographic region where specific public health concerns have been raised (e.g., the U.S. influenza surveillance system, which allows CDC to find out when and where influenza activity is occurring, track influenza-related illness, determine what influenza viruses are circulating, detect changes in influenza viruses, and measure the impact influenza is having on hospitalizations and deaths in the United States);
- Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency;
- Surveillance activities designed to enable a public health authority to locate the range and source of a disease outbreak or to identify cases of a disease outbreak;
- Surveillance activities designed to enable a public health authority to detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health, such as a natural or man-made disaster.

On the other hand, subsequent research using information collected during a public health surveillance activity, for instance genetic analysis of biospecimens, would not fall under this exclusion, but would likely be covered under one or more of the other exclusions for low-risk research or exemptions.

Additional examples of activities that would not fall under the exclusion include: exploratory studies designed to better understand risk factors, including genetic predisposition, for chronic diseases; exploratory studies designed elucidate the relationships between biomarkers of exposure and biomarkers of disease; exploratory studies of potential relationships between behavioral factors (e.g., diet) and indicators of environmental exposures. These types of activities would be considered research, and thus subject to the Common Rule, even if conducted by a Federal agency with a public health mandate. To clarify this proposed exclusion the NPRM also proposes a new regulatory definition of public health authority proposed in §__.102(k).

2). Question for Public Comment

8. Public comment is requested on whether the parameters of the exclusions are sufficiently clear to provide the necessary operational guidance, or whether any additional criteria or parameters should be applied to clarify or narrow any of these exclusions.

vi. Intelligence Surveillance Activities (NPRM at §___.101(b)(1)(vi))

1). NPRM Proposal

The sixth category of excluded activities that will not be considered research involves surveys, interviews, surveillance activities and related analyses, or the collection and use of biospecimens where these activities are conducted by a defense, national security, or homeland security authority solely for authorized intelligence, homeland security, defense, or other national security purposes.

The rationale for excluding the defense or national security-related activities is similar to that described above regarding public health surveillance activities. The lawful conduct of the departments' and agencies' mandated missions for actively protecting national security, homeland security, and homeland defense are fundamentally not research. These activities may incorporate the collection and analysis of identifiable information, but they are not designed to develop or contribute to generalizable knowledge; rather, they are solely conducted to fulfill a department or agency's legal mandate to ensure the safety and protection of the United States, its people, and its national security interests. This exclusion codifies the current interpretation of the Common Rule. Research conducted or sponsored by Federal departments and agencies using this exclusion will continue to be subject to this regulation.

b. Exclusion of Activities that are Low-risk and Already Subject to Independent Controls (NPRM at §___.101(b)(2))

i. NPRM Goals

The NPRM proposes to exclude four categories of research activities that do not entail physical risk and are non-intrusive, either in themselves or because they are subject to policies that provide oversight independent of the Common Rule. Although the activities are research, they will not be required to receive any form of determination or IRB approval—including expedited review. Additionally, statements of purpose, benefit, and voluntariness as well as consent are not required unless the entity conducting the research, collecting data, or providing data is also subject to separate statutes and regulations requiring such statements. Some of the activities proposed for exclusion are categories that appear as exemptions in the current Rule. It is proposed that the marginal protections provided by the Common Rule are not consistent with the amount of researcher time and institutional resources that they currently draw.

By reclassifying certain research activities from being exempt to being excluded, the proposed rule would eliminate the need for any administrative or IRB review. All investigators performing excluded studies are expected to act in a way that is consistent with the principles outlined in the Belmont Report, even if the Common Rule does not impose requirements on excluded work. For instance, consistent with the spirit of respect for persons, investigators should tell prospective subjects the purpose of the information collection and, where appropriate, that they can choose to participate or not in these activities, although investigators are not explicitly required to do so.

Designating certain research fully outside of the bounds of the Common Rule means that investigators are self-determining whether their own research is covered by the law. As such, the proposal to add these categories is based on the assumption that all investigators will be

accurately determining whether their proposed activity is outside the scope of the Common Rule. There is no current proposal outlining how decisions will be made for determining whether a research activity is eligible for exclusion and by whom or how differences among collaborators would be handled. As readers review each of the exclusion categories below, please consider whether the benefits associated with reducing the delay for researchers are countervailed by potential increases in risk of harm.

Throughout this NPRM, the term "low-risk" is used to denote research activities that do not entail physical risk, and where both the probability and magnitude of other risks, once required protections are applied, are hypothesized to be low. Public comment is sought on whether there are instances in the regulatory text where the term "low-risk" is used, but these conditions do not apply, and whether there is a better way to characterize this category of risk.

ii. ANPRM Discussion

The ANPRM discussed criticisms of the current rule that it does not adequately calibrate the review process to the level of risk of the research, particularly in social and behavioral research. It also discussed whether answering questions should be sufficient indication of willingness to participate in survey or interview research. It distinguished between informational or psychological risks and physical risks, and raised questions about how effectively IRB review provides protections from informational or psychological risks.

iii. Educational Tests, Survey Procedures, Interview Procedures, or Observation of Public Behaviors (NPRM at §___.101(b)(2)(i))

1). NPRM Proposal

The exclusion at §__.101(b)(2)(i) is for research, not including interventions, that involves the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) uninfluenced by the investigators, if at least one of the following is met:

- The information is recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects; or
- Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
- The research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq., research information will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, and all of the information collected, used, or generated as part of the research will be maintained in a system or systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a.

The exclusion does not include research activities in which any sort of intervention is used, in addition to the specified methods of information collection. Also, the term "survey" as used here refers to information collected about individuals via questionnaire or similar procedures (e.g., the Current Population Survey conducted by the Census). "Human subjects" do not include organizations or businesses. "Survey," as used here, does not include the collection of biospecimens or other types of information collection that might involve invasive procedures. Thus, a survey that included information collections in addition to verbal or written responses, including the collection of a biospecimen or the use of some other physically invasive procedures (e.g., a diagnostic test and blood spot or buccal swab) could not use this exclusion.

This exclusion includes the research activities in current exemption category 2 in the (current Common Rule at §__.101(b)(2)), and some additional government information collection research activities using the same methods. As in the current exemption category 2, this proposed exclusion includes research studies whose methods consist of the use of educational tests, survey procedures or interview procedures, or observation of public behavior uninfluenced by the investigators, if the data are recorded anonymously, or the information is recorded with identifiers, but is not sensitive such that its disclosure could result in harm to the subjects. The exclusion provides a list of the specific harms that must be considered, which is the same as in the current exemption category, with the addition of the specific harm of being damaging to the subjects' educational advancement. This potential harm has been added because of the obvious relevance to the effects of the disclosure of responses in research involving educational tests.

This proposed exclusion does not include the first element in the current exemption category at §__.101(b)(3)(i), which is the element pertaining to research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior if the human subjects are elected or appointed public officials or candidates for public office. The rationale for this change in the proposed NPRM is that it does not seem appropriate to single out this category of subjects for different treatment in this way.

The third element of this proposed exclusion covers research activities using the same methods identified above even when the data are recorded with identifiers and the information recorded may be personally sensitive or private but not explicitly damaging to an individual, if the research is subject to specified federal statutes and regulations that require data security and subject privacy protections. Under this proposal, the preponderance of research conducted by Federal employees and contractors that collects information exclusively through educational tests, questionnaires, or observations of behavior would no longer be subject to the Common Rule because most such collections would be subject to the Paperwork Reduction Act of 1995, would be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, and all of the information collected, used, or generated as part of the research would be maintained in a system or systems of records subject to the Privacy Act of 1974. Furthermore, consistent with these laws, OMB's Standard 2.2 in its "Standards and Guidelines for Statistical Surveys"[46] identifies the required notifications to potential survey respondents.

[46] Executive Office of the President, OMB. (Sept. 2006). Standards and Guidelines for Statistical Surveys. Retrieved from The White House: https://www.whitehouse.gov/sites/default/files/omb/inforeg/statpolicy/standards_stat_surveys.pdf.

Specifically, Standard 2.2 states that Federal agencies must ensure that each information collection instrument clearly states the reasons the information is planned to be collected; the way such information is planned to be used to further the proper performance of the functions of the agency; whether responses to the collection of information are voluntary or mandatory (citing authority); the nature and extent of confidentiality to be provided, if any (citing authority); an estimate of the average respondent burden together with a request that the public direct to the agency any comments concerning the accuracy of this burden estimate and any suggestions for reducing this burden; the OMB control number; and a statement that an agency may not conduct and a person is not required to respond to an information collection request unless it displays a currently valid OMB control number. These policies are rooted in the Fair Information Practice Principles that cover the following concepts: individual participation, transparency, authority, purpose specification and use limitation, minimization, access and amendment, redress, quality and integrity, security, training, integration, and accountability. It is proposed that the information risk protections afforded by these laws and their implementing regulations are generally stronger than the privacy protections that result from IRB review, and would result in affording more uniform protections to participants.

The rationale for excluding these research activities from the Common Rule, even when the research is not otherwise subject to additional federal controls, is that consent is inherent to participation and that the risks most likely to be experienced by subjects are related to disclosure of anonymous, non-sensitive information and are thus categorized as "low." Said another way, all individuals, including vulnerable populations, would understand that actively providing

response to educational tests, surveys, or interview procedures constitutes consent to participate and that the risk associated with such participation would be related to disclosure of the information they provided. The exclusion of this type of activity rests in large part on the idea that all individuals, regardless of the setting or context in which the activity will take place, are generally familiar with common forms of educational tests, survey and interview procedures which they experience in their daily lives, and do not need additional measures to protect themselves and their privacy from investigators who seek their involvement in research activities involving these procedures.

This exclusion is based on the assumption that the activities covered by this category are largely informational, and thus the most important role that an IRB might play with respect to reducing potential harms is to ensure data security and privacy protections. Under this assumption, the proposed exclusion is consistent with the principle of respect for persons and the preservation of autonomy. In the case of observation of public behavior, even if the subject does not know that an investigator is watching his or her actions, the subject's behavior is public and could be observed by others and thus the research observation is not inappropriately intrusive. However, there are situations in which this assumption would not always hold. For instance, administration of a questionnaire or participation in a focus group on a sensitive topic may induce significant stress in some individuals, or individuals approached about taking a survey may feel compelled to participate. Whether and how the exclusion should be bounded so that the final rule achieves a balance among the principles of beneficence, autonomy, and justice is the subject of the request for comment on this proposed exclusion.

In addition, this exclusion is in keeping with one of the goals of this NPRM, namely to reduce burden on research that includes sufficient protections to research subjects. By proposing that this exclusion could be satisfied if the information to be collected is subject to the Paperwork Reduction Act of 1995, would be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, and all of the information collected, used, or generated as part of the research would be maintained in a system or systems of records subject to the Privacy Act of 1974, the NPRM notes that the privacy protections afforded by these laws are generally comparable, if not stronger, than the privacy protections that result from IRB review.

2). Questions for Public Comment

9. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

10. Public comment is sought on whether this exclusion should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, please comment on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, ability to opt-out, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

11. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

12. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

13. Public comment is sought regarding whether these exclusions should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exclusion? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.

14. For activities captured under the third element of this exclusion, do the statutory, regulatory, and other policy requirements cited provide enough oversight and protection that being subject to expedited review under the Common Rule would produce minimal additional subject protections? If so, should the exclusion be broadened to also cover secondary analysis of information collected pursuant to such activities?

15. Public comment is requested on the extent to which excluding any of these research activities from the Common Rule could result an actual or perceived reduction or alteration of existing rights or protections provided to human research subjects. Are there any risks to scientific

integrity or public trust that may result from excluding these research activities from the Common Rule?

iv. Research Involving the Collection or Study of Information that has been or will be Collected (NPRM at §___.101(b)(2)(ii))

1). Current Rule

This exclusion appears in the current Common Rule as exemption category 4 (current Rule at §__.101(b)(4)). This exemption currently applies to research involving the use of existing data, documents, records, and pathological or diagnostic specimens, but only if the sources are publicly available or if the information is recorded by investigators in such a manner that subjects cannot be identified, directly or through identifiers linked to them.

2). ANPRM Discussion

The ANPRM proposed retaining this exemption as an exemption (not an exclusion). The ANPRM asked questions about whether the current limitations specified in exempt category 4 (research involving the use of existing information or biospecimens, §__.101(b)(4) in the current Rule) should be eliminated. Specifically, the ANPRM suggested that the category would be revised to eliminate the word "existing." With this elimination, the exemption would be broadened to cover the use of information or biospecimens that were or will be collected for

purposes other than the suggested research, rather than requiring that all of the information or biospecimens already exist at the time the study is suggested for exemption.

3). NPRM Proposal

The second category of low-risk research activities excluded from the proposed rule is a revised version of the current Rule's exemption category 4 (current Rule at §__.101(b)(4)). The NPRM proposal is that the excluded category at §__.101(b)(2)(ii) includes research involving the collection or study of information that has been or will be acquired solely for non-research activities or was acquired for research studies other than the proposed research study when the sources are publicly available, or the information is recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects or otherwise conduct an analysis that could lead to creating individually identifiable private information.

In light of the proposed expansion of the rule to cover certain biospecimens regardless of identifiability, this category has been modified such that it does not include secondary research use of biospecimens. Many of the comments supported the discussion in the ANPRM of eliminating the requirement that the information be "existing" at the time the study was suggested for exemption. Thus, in addition to changing this category of activities from being exempted to being excluded, the proposed exclusion does not require that the data exist as of the time that the study commences, but rather is expanded to include the secondary research use of

data collected in the future for research or non-research purposes. The underlying logic behind the exclusion in proposed §__.101(b)(2)(ii) is that such research involves no direct interaction or intervention with human subjects, and any research use of the information does not impose any additional personal or informational risk to the subjects, because (1) the information is already available to the public, and so any risk it may include exists already, or (2) the information recorded by the investigator cannot be identified, and no connection to or involvement of the subjects is contemplated. Any requirements of the Common Rule would not provide additional protections to subjects, and could add substantial administrative burden on IRBs, institutions, and investigators. Creating this excluded category avoids that problem.

4). Questions for Public Comment

16. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

17. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects. Is there a way in which this exclusion should be narrowed? Public comment is also sought regarding whether activities described here should appear as an exclusion or as an exemption.

v. Research Conducted by a Government Agency using Government-Generated or Government-Collected Data (NPRM at §___.101(b)(2)(iii))

1). NPRM Proposal

The third category of low-risk research activities excluded from the proposed rule at §__.101(b)(2)(iii) is research conducted by a federal department or agency using government-generated or government-collected information obtained for non-research purposes (including criminal history data), if the information originally involved a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq., the information is maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, and all of the information collected, used, or generated as part of the research is maintained in a system or systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a. This proposed exclusion is consistent with the Federal Government's emphasis on minimizing the burden on the public and maximizing the value of the information collected by the Federal Government, while protecting participant privacy and data security[47]. This exclusion is proposed for situations in which both the original data collection and the subsequent (secondary) analysis are subject to data security, participant privacy, and notice requirements associated with the named federal statutes and regulations. As such, it does not seem that the delay imposed by obtaining a determination as "exempt" or "expedited" is likely to increase the protections provided to those who have already provided the government with information for other purposes. Public comment is requested on the extent to which

[47] United States Office of Management and Budget, February 14, 2014, Memorandum to Heads of Executive Departments and Agencies; *Guidance for Providing and Using Administrative Data for Statistical Purposes* https://www.whitehouse.gov/sites/default/files/omb/memoranda/2014/m-14-06.pdf. This guidance builds on three previously issued OMB memoranda designed to increase the value of existing data: *Sharing Data While Protecting Privacy* (M-11-02 of November 3, 2010), *Open Data Policy-Managing Information as an Asset* (M-13-13 of May 9, 2013), and *Next Steps in the Evidence and Innovation Agenda* (M-13-17 of July 26, 2013).

covering any these activities under the Common Rule would substantially add to the protections provided to human research subjects.

2). Questions for Public Comment

18. Public comment is sought on whether this or a separate exclusion should also include research involving information collected for non-research purposes by non-federal entities where there are comparable privacy safeguards established by state laws and regulations, or whether such non-federally conducted research would be covered by the proposed exemption at §__.104(e)(2).

19. Public comment is requested on the extent to which covering any of these activities under the Common Rule would substantially add to the protections provided to human research subjects.

20. Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category. If so, should documentation of any kind be generated and retained?

21. Public comment is sought regarding whether some or all of these activities should be exemptions rather than exclusions.

vi. Certain Activities Covered by HIPAA (NPRM at §___.101(b)(2)(iv))

1). ANPRM Discussion

The public was asked to comment on whether it might be useful to adopt the distinction made by the HIPAA Privacy Rule , which distinguishes between "health care operations" and "research" activities, defining "health care operations" to include, among other activities, "conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities." The public was asked to comment about this specifically in the context of quality improvement activities.

2). NPRM Proposal

The fourth category of low-risk research activities excluded from the proposed rule, found at §__.101(b)(2)(iv), covers activities that are regulated under the HIPAA Privacy Rule (i.e. covered entities). These are activities whose risks relate only to privacy and confidentiality, and are already subject to independent controls provided by HIPAA. Specifically, it is proposed that research, as it is defined in this proposed rule, that involves the use of protected health information by a HIPAA covered entity for "health care operations," "public health activities," or "research," as those three terms are defined under the HIPAA Rules, would be excluded from the Common Rule. This proposed exclusion would not apply if the investigator that receives and uses individually identifiable health information for a research study was not covered by the HIPAA Rules, even if the entity disclosing the individually identifiable health information to the investigator was covered by the HIPAA Rules. The exclusion is limited in this way to ensure that

it only applies to research studies and information that are already subject to independent privacy, confidentiality, and security protections.

A majority of comments on the 2011 ANPRM favored distinguishing between research and health care operations, as such terms are defined in the HIPAA Privacy Rule and the Health Information Technology for Economic and Clinical Health (HITECH) Act, and excluding the latter from the policy. Some commenters noted that people involved in these various activities are protected in other ways, and alluded to the sorts of measures that provide protection. Others suggested that any exclusions should be limited to data collection and analysis activities, or to activities below a certain threshold of risk (i.e., minimal risk). A minority of comments objected to these exclusions, arguing that these activities represent encroachments on their individual rights and privacy, and that oversight in accordance with the Common Rule requirements would be more protective. The proposed exclusion excludes only certain activities that involve data collection and analysis, where privacy safeguards are in place.

3). Questions for Public Comment

22. Public comment is requested on whether the protections provided by the HIPAA Rules for identifiable health information used for health care operations, public health activities, and research activities are sufficient to protect human subjects involved in such activities, and whether the current process of seeking IRB approval meaningfully adds to the protection of human subjects involved in such research studies.

23. Public comment is sought regarding to what extent the HIPAA Rules and HITECH adequately address the beneficence, autonomy, and justice aspects for the collection of new information (versus information collected or generated in the course of clinical practice, e.g., examination, treatment, and prevention). Should this exclusion be limited to data collected or generated in the course of clinical practice? If additional data collection is allowable, should it be limited to what is on the proposed Secretary's list of minimal risk activities (discussed in more detail below in II.F.2 of this preamble)?

24. Public comment is requested on whether additional or fewer activities regulated under the HIPAA Privacy Rule should be included in this exclusion.

c. Applicability of Exclusions to the Subparts

i. Current Rule

The current Common Rule does not contain exclusion categories, though as discussed above, some of the proposed exclusions are similar to activities that are exempt under the current regulations, which therefore might provide a basis for comparison.

All of the current exemption categories can be applied to research that is subject to subpart B. None of the current exemption categories can be applied to research that is subject to subpart C.

The exemptions in the current Rule generally apply to subpart D. However, the exemption at §__.101(b)(2), for research involving educational tests, survey or interview procedures, or observation of public behavior does not apply to subpart D except for research involving educational tests or observations of public behavior when the investigators do not participate in the activities being observed.

ii. NPRM Proposals

Language specifying the application of the exclusions to the subparts can be found in the NPRM at §__.101(b)(2) and (3).

It is proposed that all of the exclusion categories in §__.101(b)(2) and (3) apply to research that is subject to subpart B, and therefore the requirements imposed by subpart B would not need to be met.

It is similarly proposed that all of the exclusion categories in §__.101(b)(2) and (3) apply to research involving prisoners, therefore the requirements of subpart C would not need to be met. This would narrow the scope of research currently requiring subpart C review and certification to OHRP. Considerations in favor of this conclusion include the preponderance of low-risk socio-behavioral research designed to improve prisoner welfare, including studies that focus on substance abuse treatment, community reintegration, and services utilization; the occurrence of prisoner-subjects in research not targeting prisoner populations; the occurrence of prisoner-subjects in databases or registries; and the broad regulatory interpretation of the subpart C

"prisoner" definition. Public comment is requested on whether the application of these exclusions to research involving prisoners is appropriate and acceptable.

It is proposed that all of the exclusion categories in §__.101(b)(2) apply to research subject to subpart D, with the exception that the exclusion proposed under §__.101(b)(2)(i) would only apply to research involving educational tests or observations of public behavior when the investigator does not participate in the activities being observed. This limitation would maintain the protection currently provided by the similar application of the current exemption §__.101(b)(2) to research involving children, and would continue to require IRB review under the Common Rule and additional IRB review under subpart D of 45 CFR part 46 when the research involves surveys or interview procedures with children or observation of public behavior when the investigator participates in the activities being observed.

iii. Questions for Public Comment

25. Should research involving prisoners be allowed to use any or all of the exclusions found at §__.101(b)(2) and (3), as currently proposed?

26. Are there certain provisions within the broader categories proposed at §__.101(b)(2) and (3) to which the subparts should or should not apply?

3. Proposed Exemptions (NPRM at §__.104)

The Common Rule has been criticized for inadequately calibrating the review process to the risk of research. Some have argued that, particularly given the paucity of information suggesting significant risks to subjects in certain types of survey and interview-based research, the current system overregulates such research. Further, many critics see little evidence that most IRB review of social and behavioral research effectively protects subjects from psychological or informational risks. Overregulating social and behavioral research in general may serve to distract attention from identification of social and behavioral research studies that do pose ethical challenges and thus merit significant oversight.

The proposed exemption categories and attendant policies and procedures related to exemptions appear in the NPRM at §__.104, and are guided by the following policy goals:

- To create procedural efficiencies for IRBs, administrators and investigators in making and receiving exemption determinations, thereby reducing the overall IRB workload and the wait time for investigators to begin their work.
- To ensure that reasonable safeguards are in place for certain lower risk research activities not fully excluded under the current Common Rule by requiring that research in certain exemption categories follow elements of the proposed rule, but not be required to undergo full IRB review according to the full set of criteria at §__.111(a)(1)-(8) and other regulatory requirements of the Common Rule .

Note that all of the exemption categories in the current Rule have been carried over to the proposed Rule in one or another form. In particular, some of the current Rule's exemptions have

now become exclusions under the NPRM (and thus subject to no administrative or IRB review), while some remain in the NPRM's exempt categories section.

Under the current Common Rule, research may qualify for exemption from the regulatory policy if it falls into one of the six current categories at §__.101(b)(1)-(6). Such studies are fully exempt from the regulations. The current regulations do not specify who at an institution may determine that research is exempt under §__.101(b). However, in the past OHRP has recommended that because of the potential for conflict of interest, investigators not be given the authority to make an independent determination that human subjects research is exempt. OHRP has recommended that institutions should implement exemption policies that most effectively address the local setting and programs of research. OHRP has recognized that this may result in a variety of configurations of exemption authority, any of which are acceptable assuming compliance with applicable regulations.

The NPRM proposes to retain the term "exempt," (rather than "excused," as suggested in the ANPRM) but require that exempt research comply with certain provisions of the proposed rule such as proposed privacy safeguards at §__.105 (discussed below). This policy retains and, in important respects (through a new safe harbor provision), expands the current flexibility of institutions to develop a system in which someone at the institution—including the investigator, unless prohibited by law—uses an exemption decision tool to make the exemption determination.

It is important to recognize that while in some cases there are new requirements that have been imposed on the exemption categories that do not exist in the current version of the exemption categories, this usually does not actually represent a tightening of the rules for those exemptions. To the contrary, these changes are generally being made to allow the exemption in question to be expanded to cover activities that are not currently exempt. For example, adherence to new privacy standards is a new requirement in order for certain surveys to be exempt, but these are surveys that under the current Common Rule would require IRB review.

The proposed eight exemptions are divided into three groupings according to the kind of risk characteristically involved and what protections are called for: (1) low-risk interventions that do not require application of standards for information and biospecimen protection; (2) research that may involve sensitive information that requires application of standards for information and biospecimen protection described in proposed §__.105; and (3) secondary research involving biospecimens and identifiable private information that requires application of privacy safeguards discussed at proposed §__.105, broad consent as discussed in proposed §__.116(c), and limited IRB review as discussed in proposed §__.111(a)(9).

a. Making Exempt Research Determinations (NPRM at §__.104(c))

i. NPRM Goal

The goal of this NPRM proposal is to create procedures for appropriate exemption determinations in a manner that does not waste time and effort.

ii. Current Rule

In developing policies and procedures addressing the exemptions, OHRP currently recommends that when an exemption determination is made, the specific exemption category or categories should be included in the record of the material supplied to the IRB and this information should be available for oversight purposes. In addition, OHRP guidance has said that institutional policies and procedures should identify clearly who is responsible for making exemption decisions. OHRP notes that under current policy a Common Rule Department or Agency retains final authority as to whether a particular human subjects research study conducted or supported by that Department or Agency is exempt from the Common Rule (§__.101(c)) and that authority continues under the proposed regulations.

iii. ANPRM Discussion

The ANPRM discussed a mechanism to (1) register exempt research, and (2) audit a small but appropriate portion of such research, which would still be subject to other regulatory protections such as the suggested data security and information protection standards and certain consent requirements.

The ANPRM discussed a tracking mechanism to enable institutions to assure that such research meets the criteria for inclusion in the suggested "excused" categories. The original recommendations would require investigators to register their study with an institutional office

by completing a brief form, thus eliminating the current practice of not allowing investigators to begin conducting such studies until a reviewer had determined it meets the criteria for excused research. This would make the institution aware of key information about the research (such as the purpose of the research and the name of the study's principal investigator), without also requiring that the activity undergo a review that, if not done in a timely manner, could slow the research without adding any significant protection to subjects. In addition, the institution could choose to review some of the submissions at the time they are filed and, if deemed appropriate, require that the study be sent for expedited review or, in rare cases, convened IRB review. It would be made clear that the regulations would not require, and in fact, would discourage, having each of these registration forms undergo a comprehensive administrative or IRB review prior to commencing the study or even afterward.

The auditing requirement was intended to encourage institutions to use the regulatory flexibility suggested for the exempt categories of research. The auditing requirement would have provided institutions with information needed to assess their compliance with the new "excused" categories without unnecessarily subjecting all such research to either prospective review, or even routine review sometime after the study is begun. Note that currently, OHRP recommends that there be some type of review by someone other than the investigator to confirm that a study qualifies as exempt, and many institutions do impose such a requirement even though such a requirement is extra-regulatory.[48]

[48] Office for Human Research Protections. (2011, January 20). Exempt Research Determination FAQs. Retrieved from Frequently Asked Questions About Human Research: http://www.hhs.gov/ohrp/policy/faq/index.html,

The ANPRM also asked whether it was acceptable for investigators to independently determine whether their research was exempt, whether review of all registrations should be required, and whether there should be a time limitation or waiting period before excused research could begin. The ANPRM also asked whether it was appropriate to require institutions holding a Federalwide assurance (FWA) to conduct retrospective audits of a percentage of the excused studies to make sure they qualify for inclusion in an excused category, and if so, how such audits should be conducted.

iv. NPRM Proposal

The NPRM proposes to adopt an exemption determination documentation requirement which is somewhat different from the registration system suggested in the 2011 ANPRM. To assist investigators and institutions in making a timely and accurate determination of exemption status the NPRM at §__.104(c) states that federal departments or agencies will develop one or more exemption determination tools. Federal departments or agencies may create their own tool, or rely on a tool created by another department or agency (including the web-based tool created by HHS). The tool, which has not yet been developed, will be designed in such a way that if the person using the tool inputs accurate information about the study, the tool will produce an outcome which is the determination as to whether the study is exempt or not. Institutions may rely on use of the federally developed tool by investigators as a "safe harbor" for this determination: so long as the information that was provided to the tool was accurate, result of the application of the tool will be presumed by the federal departments or agencies to be an appropriate determination of exempt status. Use of the tool will be voluntary; each institution

and agency would determine whether to rely on the decision tool for their determinations, and if so, who would be allowed to operate it. Institutions, if they so choose, could continue to have such determinations made by an individual who is knowledgeable about the exemption categories and who has access to sufficient information to make an informed and reasonable determination. In general, it is expected that investigators would not be allowed to make exemption determinations for themselves without the use of the decision tool, due to considerations of a conflict of interest. It should also be noted that for FDA-regulated device studies IRB review is required by statute.

The NPRM also proposes that the institution or IRB be required to maintain records of exemption determinations, which records must include, at a minimum, the name of the research study, the name of the investigator, and the exemption category applied to the research study. Maintenance of the output of the completed decision tool would fulfill this recordkeeping requirement.

In general, commenters to the 2011 ANPRM were not necessarily opposed to the concept of registration but sought further information on what this process would entail. Public commenters also expressed concerns about allowing an investigator to independently make the determination that his or her research is exempt. Other commenters suggested that this practice would be acceptable for some investigators, whose research is well known to IRB members, and is clearly within an exempt category. The ANPRM noted concerns that some exempt research was unnecessarily delayed by requirements of some institutions to review the research to make an exemption decision.

Several institutions reported that they already as a matter of policy require investigators to submit exempt studies to the IRB, not necessarily for full board review, but to ensure that the exempt determination is valid. These decisions typically are made by the IRB administrator and never involve full review unless there is concern about the exemption status. Thus, they felt the registration requirement was unnecessary and would add new administrative burdens for research already considered low-risk.

Other commenters, such as investigators conducting research currently considered exempt, were strongly opposed to a registration requirement because it would add a new burden to conducting less than minimal risk and exempt research. In addition, commenters raised concerns about the administrative burden and need for a retrospective audit system of registered research.

This NPRM proposal is anticipated to provide more flexibility than the registration requirement originally proposed, while helping to ensure that correct determinations of exempt status are made. The existence of a "safe harbor" mechanism will hopefully encourage institutions to create policies that allow investigators to use the tool, and thus to be able to more quickly commence their research without needing additional administrative or IRB reviews for these types of studies. Other people at the institution who have access to accurate information about a proposed study may also utilize the tool, which will also allow research to go forward unimpeded.

In addition, it is proposed that a change to §__.109(a) be made to clarify that the Common Rule does not give IRBs the authority to review or approve, require modification in or disapprove research that qualifies for exemption under §__.104(d), (e), or (f)(2).

There is no auditing requirement in this NPRM proposal. Consequently, it does not address concerns raised at the ANPRM stage regarding potential conflict of interest if the investigator is providing the information to operate the decision tool. Public comment is sought on this idea regarding the operational details for further development of this proposal. Depending upon the comments received on this proposal, additional operational details regarding the proposed federally sponsored decision tool would be developed and subject to public comment. It should also be noted that the lack of an auditing requirement would not prohibit an institution from performing post-approval monitoring of exemption determinations according to the institution's standard operating procedure.

v. Questions for Public Comment

27. Public comment is sought regarding how likely it would be that institutions would allow an investigator to independently make an exempt determination for his or her own research without additional review by an individual who is not involved in the research and immersed in human research protection e.g., a member of the IRB Staff.

28. Public comment is sought regarding whether an investigator would be able to contrive his or her responses to the automated exemption decision tool in order to receive a desired result i.e., an exempt determination, even if it does not accurately reflect the research activities.

29. Public comment is sought on whether it would be more appropriate for some of the exempt categories than others to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

30. Public comment is sought regarding whether relying on the exemption determination produced by the decision tool where investigators themselves input the data into the tool as proposed would reduce public trust in research.

31. Public comment is sought regarding how likely it would be that institutions would rely on such a decision tool to provide a safe harbor for an investigator making a determination that the proposed research qualifies for an exemption, or whether developing such a tool would not be worthwhile, and whether institutions would be able to adequately manage exemption determinations without the use of the decision tool.

32. Public comment is sought regarding what additional information should be required to be kept as a record other than the information submitted into the decision tool, for example, a study abstract, the privacy safeguards to be employed, or any notice or consent document that will be provided.

33. Public comment is sought regarding the value of adding an auditing requirement.

b. Exemptions Subject to the Documentation Requirements of §__.104(c) and No Other Section of the Proposed Rule

Four exemptions are proposed that will not be subject to any additional requirements apart from the need to keep a record of the determination that the study was exempt. Three of these four exemptions in proposed §__.104(d) are versions of exemptions found in the current rule. A revised version of exemption category 1 in the current Common Rule (research conducted in established or commonly accepted educational settings) is found at proposed §__.104(d)(1) in the NPRM. A revised version of the current exemption category 5 (research and demonstration projects) is found at proposed §__.104(d)(2). Exemption category 6 in the current Common Rule (taste and food quality evaluations) is found in the NPRM at §__.104(d)(4), and is unchanged.

i. Research Conducted in Established or Commonly Accepted Educational Settings (NPRM at §__.104(d)(1); current Rule at §__.101(b)(1))

1). NPRM Goal

The goal is to retain an exemption for a considerable portion of education research, but to provide for review if the research might adversely affect students' opportunity to learn required educational content, or the assessment of educators.

2). Current Rule

The current exemption category 1 (§__.101(b)(1) in the current Rule) is for research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

3). NPRM Proposal

The first exemption category is for research conducted in established or commonly accepted educational settings when it specifically involves normal educational practices. This includes most research on regular and special education instructional strategies, and research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods, so long as the research is not likely to adversely impact students' opportunity to learn required educational content in that educational setting or the assessment of educators who provide instruction.

This exemption category is a revised version of the first exemption category in the current Common Rule. The rationale for the revision is that there are concerns about whether the conduct of some research projects of this type might draw sufficient time and attention away from the delivery of the regular educational curriculum, and thereby have a detrimental effect on

student achievement. The current education system places a strong emphasis on student performance on tests in core curriculum areas such as reading, science, and mathematics, which have a significant effect on such things as grade promotion and student assignment to different courses, and cumulatively influence student attainment and achievement. It could also have a negative effect on teachers being evaluated on the basis of student performance. The exemption category is designed to not include such research projects. Otherwise, the exemption is retained in order to allow for the conduct of education research that may contribute to the important public good of improving education, consistent with the principle of beneficence.

4). Questions for Public Comment

34. Public comment is sought on whether this exemption category should only apply to research activities in which notice that the information collected will be used for research purposes is given to prospective subjects or their legally authorized representatives as a regulatory requirement, when not already required under the Privacy Act of 1974. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose, privacy safeguards, contact information, etc. Comment is also sought on how such a notice should be delivered, e.g., publication in a newspaper or posting in a public place such as the school where the research is taking place, or by individual email or postal delivery. Note that other requirements, such as those of the Family Educational Rights and Privacy Act (FERPA) or the Protection of Pupil Rights Amendment, may also apply. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

35. Public comment is sought on whether the privacy safeguards of §__.105 should apply to the research included in §__.104(d)(1), given that such research may involve risk of disclosure of identifiable private information.

ii. Research and Demonstration Projects Conducted or Supported by a Federal Department or Agency (NPRM at §__.104(d)(2); current Rule at §__.101(b)(5))

1). NPRM Goal

The NPRM exemption proposed at §__.104(d)(2) is for research and demonstration projects involving public benefit or service programs, and is a slightly revised version of exemption 5 in the current Common Rule.

The proposed regulatory revision and change in interpretation of the exemption is designed to clarify the scope of the exemption so that more research studies would be exempt. It is believed that these changes would make the exemptions easier to apply. It is also designed to allow the Federal Government to carry out important evaluations of its public benefit and service programs to ensure that those programs are cost effective and deliver social goods, consistent with the principle of beneficence.

2). Current Rule

The current version of this exemption category was originally created based on the recognition that alternative processes are in place in which ethical issues raised by research in public benefit or service programs are be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal laws. These alternative processes implicitly consider risk, but there is not a predefined scope for the likelihood or magnitude of risk in these research activities. In fact, the Secretary of HHS noted in1983 that these demonstration and service projects are already subject to procedures which provide for extensive review by high level officials in various program administration offices. The Secretary further noted that review by an IRB would be duplicative and burdensome to state and local agencies and to other entities participating in demonstration projects. It was thought that removal of this unnecessary layer of review would not only reduce the cost of the projects but also help avoid unnecessary delays in project implementation.[49]

OHRP has interpreted the current exemption category 5 (§__.101(b)(5) in the current Common Rule) to apply only to those research and demonstration projects designed to study a "public benefit or service program" that a Common Rule department or agency itself administers, and for which the public benefit or service program exists independent of any research initiative. As an example, OHRP has in the past said that a research study to evaluate a Centers for Medicare & Medicaid Services (CMS)-administered demonstration project comparing two different mechanisms for reimbursing providers under Medicare or Medicaid would meet this exemption. However, this exemption would not apply to some types of research, for example, the evaluation of clinical trials (e.g., a National of Institutes of Health-funded clinical trial comparing two

[49] 48 FR 9266 (Mar. 4,1983).

treatment regimens for heart disease), even if such studies would inform Medicare reimbursement policies.

3). ANPRM Discussion

The ANPRM asked several questions about the interpretation and applicability of current exemption category 5 (current Common Rule at §__.101(b)(5)), including the scope of the current interpretation of the category 5 exemption. The ANPRM also asked if the current category 5 guidance entitled, "OPRR Guidance on 45 CFR 46.101(b)(5),"[50] should be revised, or if additional guidance on the interpretation of exemption category 5 is needed.

More specifically, the ANPRM asked whether this exemption should be revised to assure that it is not misinterpreted or misapplied, whether broadening it would result in inappropriately increasing risks to subjects, how such risks might be mitigated, and whether OHRP guidance should be revised.

4). NPRM Proposal

The second proposed exemption category (NPRM at §__.104(d)(2)) is for research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those

[50] *See* 48 FR 9266-9270 (Mar 4, 1983). (OPRR Guidance on 45 CFR 46.101(b)(5), Exemption for Research and Demonstration Projects on Public Benefit and Service Programs, http://www.hhs.gov/ohrp/policy/exmpt-pb.html)

programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.

It is proposed that each federal department or agency conducting or supporting the research and demonstration projects would be required to establish, on a publicly accessible federal website or in such other manner as the department or agency head may prescribe, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project would be required to be published on this list prior to or upon commencement of the research. Agencies and departments would be able to create or use their own websites for this purpose, or use a website created by OHRP. Note that for studies exempted pursuant to §__.104(d)(2), the recordkeeping requirement at proposed §__.104(c) would be deemed to be satisfied by the published list required under proposed §__.104(d)(2)(i).

There were few responses to the questions posed on this exemption in the 2011 ANPRM. However, those that did comment noted that this category is often misunderstood by IRBs and, at best, would benefit from clearer guidance. Commenters said that examples would help investigators and IRBs understand when research activities included in demonstration projects constitute human subjects research subject to the Common Rule. Commenters noted that many activities in demonstration projects do not contribute to generalizable knowledge as they produce results that are relevant only to the program being assessed; as such, many of these activities do not meet the Common Rule's regulatory definition of "research" and thus fall outside of the rule. Other commenters said that some activities in this category are mandated or required by law or

regulation and should not be considered to be under the purview of the Common Rule. It was noted that the critical issue in these studies should be protecting privacy and as long as measures are in place to do so, additional protections are not required.

The revision of the language in this exemption clarifies the original language to say that a federally conducted project examining any aspect of a public benefit or service program would qualify for the exemption. The clauses concerning procedures for obtaining benefits, other changes in programs and procedures, and changes in methods or levels of payment are merely examples of such projects, and are not considered to be all-inclusive.

In addition, OHRP proposes to clarify its interpretation of public benefit and service programs which are being evaluated as part of the research to include public benefit or service programs that a Common Rule department or agency does not itself administer through its own employees or agents, but rather funds (i.e., supports) through a grant or contract program. Therefore, the exemption would be clarified to apply to research and demonstration projects supported through federal grants or cooperative agreements, for example. These activities include appropriate privacy, confidentiality and security safeguards for any biospecimen and information used in this research. For example, information collected in some demonstration projects are subject to the protections of the HIPAA rules, and Federal agencies include conditions in grants or cooperative agreements which require the recipient to protect the confidentiality of all project-related information that includes personally identifying information.

It is believed that these changes would make the exemptions easier to apply. It is also designed to allow the Federal Government to carry out important evaluations of its public benefit and service programs to ensure that those programs are cost effective and deliver social goods. The proposed changes to this exemption would require OHRP to revise its existing guidance document on this exemption accordingly.

These changes would bring the language into conformance with other provisions of the rule that refer to research "conducted or supported" by Federal agencies. Both current practice and the edited language cover such research, whether it is conducted directly by federal staff or through a contract, cooperative agreement, or grant. These methods of administration are, of course, always subject to department or agency head approval, directly or by delegation. In addition, some of these research and demonstration projects are conducted through waivers, interagency agreements, or other methods that also require agency head approval. Accordingly, both the previous and the revised language allow for the full panoply of methods by which research and demonstration projects on public benefit or service programs can be carried out.

Although research such as that described above is exempt, an additional requirement is proposed. In the interest of transparency, each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible federal website or in such other manner as the Secretary may prescribe, a list of the research and demonstration projects which the federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to or upon commencement of the research. The agency determines what will be included on this list and maintains its

oversight. Agencies that already publish research and demonstration projects on a publicly accessible website could satisfy this proposed requirement if the existing website were to include a statement indicating which of the studies were determined to meet this exemption. The goal of this proposed requirement is to promote transparency of federally conducted or supported activities affecting the public that are not subject to oversight under the Common Rule. It should not create any delay to the research. HHS will develop a resource that all Common Rule agencies may use to satisfy the requirement at proposed §__.104(d)(2)(i). Alternatively, an agency can make its own website.

Currently, there is no such comprehensive listing of studies that have been determined to have met this exemption, so this requirement would also enable Common Rule departments and agencies to better assess the types of projects that use this exemption, and consider whether any changes to its scope would be appropriate.

5). Questions for Public Comment

36. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, e.g., the research purpose, privacy safeguards, or contact information. Also comment on how such a notice should be delivered; e.g., publication in a newspaper or posting in a public place, or by individual email or postal delivery. Would requiring notice as a condition of this exempt research strike a good balance between autonomy

and beneficence? In many cases, it may be that individual notice or consent to all potentially affected persons before the research or demonstration commences is ordinarily impossible in the conduct of such studies. For example, if a research or demonstration project will affect all inhabitants of a large geographic area (e.g., a housing, a police patrol, a traffic control, or emergency response experiment), or all clients or employees of a particular program or organization or setting will be subject to a new procedure being tested (e.g. a new approach to improving student performance, a new anti-smoking or anti-obesity program, a new method for evaluating employee performance), would it be possible to make participation voluntary for all affected individuals, or even to identify and inform all affected individuals in advance?

37. Public comment is sought on whether this exemption category is appropriate based on the recognition that alternative processes are in place in which ethical issues raised by research in public benefit or service programs would be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal laws, rather than meeting specific risk-based criteria, or whether risk limitations should be included, and if so, what those limitations should be. Though long-standing, this exemption has never identified specific risk-based criteria, or risk limitations to bound the type of projects that may be covered. When originally promulgated, the exemption did stipulate that following the review of such projects, if the Secretary determines that the research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject, then written informed consent would be required. Public comment is sought on whether to limit the risk that can be imposed on subjects while using this exemption, and if so, how to characterize those limits in a

clear fashion. If more than minimal risk interventions are included, public comment is sought on whether, for transparency, this should be made clear in the regulatory text.

With regard to the issue of risks encountered by participants in such research or demonstration projects, comments are also sought regarding the argument that any and every demonstration project involving changes in public benefit or service programs (e.g., water or sewage treatment programs or pollution control programs, programs involving educational procedures, or programs involving emergency procedures related to extreme weather events, etc.) exposes those affected to possible risks of some kind. In this regard, those risks are ordinarily and perhaps always no different in kind or magnitude than those involved in simply making the change in procedures without using research tools to evaluate them. For example, health care providers could be required to perform certain sanitation reforms to prevent patient infections whether or not such reforms were first tested in practice through a research or demonstration project. It is common for all Federal departments and agencies that regulate private or public organizations to impose conditions of participation in public programs providing for safety, program integrity, financial reporting, etc. Public comment is sought regarding whether there should be conditions (e.g., an individual notice or consent requirement) imposed on such research or demonstration projects involving public benefit or service programs which might lead to significant impediments or limitations on testing and evaluation before or after being imposed program-wide. Would the effect of imposing expensive or impracticable conditions on public benefits or services evaluations be to reduce the number of such evaluations and consequently to expose program participants to increased risk through exposure to untested reforms?

38. Public comment is sought on whether the existing privacy safeguards for such activities, including the Privacy Act, HIPAA rules, and other federal or state privacy safeguards provide sufficient independent controls, or whether other safeguards such as the privacy safeguards of §__.105 should be applied.

iii. Research involving benign interventions in conjunction with the collection of data from an adult subject (NPRM at §__.104(d)(3))

1). NPRM Goal

The goal of this proposed new exemption for studies that involve benign interventions is to eliminate IRB review of these low-risk studies to reduce time and effort, allow IRBs to focus more attention on research with higher risks or presenting other ethical challenges, and to enable this research to go forward.

2). Current Rule

Currently, research studies in the social and behavioral sciences that do not qualify for exemption category 2 (current Common Rule at §__.101(b)(2)), but that involve certain types of well-understood interactions with subjects (e.g., asking someone to watch a video and then conducting word association tests), require either convened board or expedited IRB review.

3). ANPRM Discussion

The ANPRM considered whether to include on the list of exempt studies certain types of social and behavioral research conducted with competent adults that would involve specified types of benign interventions commonly used in social and behavioral research, that are known to involve virtually no risk to subjects, and for which prior review does little to increase protections to subjects. These would be methodologies that are familiar to people in everyday life and in which verbal or similar responses would constitute the research data being collected. The ANPRM asked whether this category should include research in which there is deception.

4). NPRM Proposal

The proposed exemption at §__.104(d)(3) is new and includes research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses (including data entry) or video recording if the subject prospectively agrees to the intervention and data collection and at least one of the following is met:

- The information obtained is recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects; or
- Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

For the purpose of this proposed provision, benign interventions would be brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and it would be required that the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. If these criteria were met, such benign interventions might include research activities in which a subject is asked to read materials, review pictures or videos, play online games, solve puzzles, or perform cognitive tasks. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption would not be applicable unless the subject authorizes the deception. For the purpose of this proposed provision, authorized deception would be prospective agreement by the subject to participate in research where the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Many commenters to the 2011 ANPRM supported adding another exemption category of research for certain types of social and behavioral activities, conducted with competent adults, that would involve specified types of benign interventions beyond educational tests, surveys, focus groups, interviews, and similar procedures that are commonly used in social and behavioral research, that are known to involve virtually no risk to subjects, and for which IRB review does little to increase protections for subjects. However, many commenters were opposed to the requirement that subjects be "competent adults" in order for the expanded exemption to apply, asking whether tests of competency would be required for such research to proceed.

This new exemption category addresses research involving benign interventions, in which information is collected through verbal or written responses and recorded in a manner such that human subjects cannot be identified, or where the disclosure of responses would not place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation. Here, a "benign intervention" is categorized as one that is temporary and painless, producing no lasting negative impacts. Examples of benign interventions might include research activities in which a subject is asked to read materials, review pictures or videos, play online games, solve puzzles, or perform cognitive tasks, so long as the interventions meet the requirements for this category.

The NPRM proposes to allow this type of research to occur without the requirements of informed consent or data security protections because neither the intervention nor the identifiability of the information is likely to result in harm to the subject, and the subject must prospectively agree to the intervention and the data collection. This exemption would include some research using authorized deception, where there is a prospective agreement by the research subject to participate in the activity after being informed that he or she will be unaware or misled regarding the nature of the research (§__.104(d)(3)(iii)-(iv)). Subjects must be adults, but the provision does not specify that they must be competent, and so tests of competency are not necessary; however, the presumption is that in keeping with the principle of respect for persons, these subjects will not be taken advantage of. This new exemption category is being added because respect for persons is accomplished through the prospective subject's prospective agreement or authorization, the research activities pose little risk to subjects, and the use of this

exemption for many social or behavioral studies will enable IRBs to devote more time and attention to research studies involving greater risks or ethical challenges.

5). Questions for Public Comment

39. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose (if authorized deception is not utilized), privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

40. Public comment is sought regarding what improvements could be made to the language describing the type of interventions in this exemption category so as to make clear what interventions would or would not satisfy this exemption category.

41. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.

iv. Taste and Food Quality Evaluation and Consumer Acceptance Studies (NPRM at §__.104(d)(4); current Rule at §__.101(b)(6))

The exemption proposed in §__.104(d)(4) is found in the current Common Rule at §__.101(b)(6). This exemption is for taste and food quality evaluation and consumer acceptance studies if wholesome foods without additives are consumed, or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by FDA or approved by the EPA or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

This exemption is retained unchanged from the current Common Rule. The research activities included under this intervention are relatively benign, no sensitive information is collected, and presumably subjects are made aware of the nature of the activity before they participate, and may exercise their autonomy in choosing whether or not to participate. However, since the research activities involve physical interventions with the subject, the rules relating to exemption determinations and the record-keeping requirement for exempt activities are appropriate.

1). Question for Public Comment

42. Public comment is sought on whether this exemption category should be narrowed to apply only to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a

good balance between autonomy and beneficence? Should prospective subjects be given the explicit opportunity to opt out of such research?

c. Exemptions Subject to the Documentation Requirements of §__.104(c) and the Privacy Safeguards Described in §__.105

Two exemption categories are proposed which will be subject to the documentation requirement and the new privacy safeguards. The first exemption category is for certain research involving educational tests, surveys, interviews, or observation of public behavior. The second category is for secondary research use of identifiable private information originally collected for non-research purposes where notice was given.

One of the functions of IRB review when a study presents only informational risks is to ensure the sufficiency of the investigator's plan for protecting any identifiable private information that will be collected, created, or used as part of the study. In keeping with one of the goals of this NPRM and as discussed in section II.A.3 of this preamble, to reduce burden associated with research that includes sufficient protections to research subjects, this NPRM proposes to eliminate the need for IRB review for studies involving the collection of identifiable private information when collected through educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording), or in studies involving only the secondary analysis of identifiable private information originally collected for non-research purposes when the proposed privacy safeguards at §__.105 are met. The newly proposed §__.105 offers three avenues to

meeting the data security and privacy protection requirements, all three of which are posited to be at least as protective as those usually that result from IRB review.

- The investigator is required by law to comply with, or voluntarily complies with, the HIPAA Rules;
- The activity is conducted by federal departments and agencies, and the activity is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and the research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.; or
- The investigator complies with the privacy safeguards promulgated by the Secretary of HHS (which standards will be designed so that they could be readily implemented by an individual investigator, and would involve minimal cost and effort to implement).

It is believed that the protections afforded by the Paperwork Reduction Act, section 208 of the E-Government Act, and the Privacy Act in combination with each other are generally equivalent to the privacy protections that result from IRB review. It is similarly believed that the privacy protections afforded by HIPAA in the context of the studies exempted under §__.104(e) justify eliminating IRB review.

The proposed section 105 also includes limitations on the use, release, and disclosure of the identifiable private information collected or maintained for research subject to this Rule.

Although most if not all of these requirements are already in effect for federal entities and HIPAA covered entities, they will likely be new to some institutions and their investigators. The intent is that Secretary would develop a list of "reasonable and appropriate safeguards" that would be easily implemented by investigators. As such, it is envisioned that the Secretary's privacy safeguards described in proposed §__.105 would be designed as a checklist that could be easily monitored by investigators and IRB members alike. In the case where IRB members have additional expertise, they may choose to deviate from the Secretary's list. Acknowledging that it is difficult for the public to fully comment on the implications of such a checklist before it has been developed; the Rule includes a requirement that the Secretary solicit public comment on the proposed minimum safeguards.

i. Questions for Public Comment

43. Public comment is sought on the concept of requiring such minimum safeguards and limitations on disclosure, as well as whether the requirements of the proposed §__.105 would constitute a broadening of IRB responsibilities rather than a streamlining of the implementation of responsibilities that many IRBs already adopted. If an institution does view this as an inordinate broadening of responsibilities, does the institution currently have in place alternative mechanisms for ensuring data security and participant privacy in a research context? Suggestions

for alternative approaches to meeting public expectation that federally sponsored research safeguard their data and protect privacy are sought during this public comment period.

44. Public comment is sought regarding whether the proposed Rule's information security requirements for biological specimens and identifiable private information are highly technical and require a level of expertise not currently available to most IRBs. Do these security requirements unrealistically expand IRB responsibilities beyond current competencies?

ii. Research Involving Educational Tests, Surveys, Interviews, or Observation of Public Behavior if the Information is Recorded with Identifiers and even if the Information is Sensitive (NPRM at §__.104(e)(1))

1) NPRM Goals

The goal of the proposed exemption at §__.104(e)(1) is to eliminate the need for IRB review of certain low-risk studies that involve collecting information by means of educational tests, surveys, interviews, or observation of public behavior. The intent is that this change would reduce IRB and investigator time and effort in reviewing and submitting protocols, and would allow IRBs to focus more attention on research with higher risks or presenting other ethical challenges, would respect autonomy, and would enable this research to go forward.

2) Current Rule

The current Common Rule only allows these activities, involving the recording of identifiable information about research subjects, to be exempt if the disclosure of the identifiable information outside the research could not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

3) ANPRM Discussion

The ANPRM discussed criticisms of the current Common Rule that it does not adequately calibrate the review process to the level of risk of the research, particularly in social and behavioral research. It also discussed whether answering questions should be sufficient indication of willingness to participate in survey or interview research. It distinguished between informational or psychological risks and physical risks, and raised questions about how effectively IRB review provides protections from informational or psychological risks.

Specifically, the ANPRM discussed expanding the current exemption category 2 (current Rule at §___.101(b)(2)) to include all studies involving educational tests, surveys, interviews, and similar procedures, so long as the subjects are competent adults, without any further qualifications (but subject to the data security and information protection standards).

4) NPRM Proposal

The exemption proposed in §__.104(e)(1) covers research, not including interventions, involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures,

interview procedures or observation of public behavior (including visual or auditory recording), if the information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects. The research in this category is exempt from most requirements of the NPRM, but investigators must adhere to the privacy safeguards outlined in proposed §__.105. Note that the language used in this exemption is very similar to that used in the current exemption 2, proposed exclusion §__.101(b)(2)(i), and the proposed exemption at §__.104(d)(3); unlike the language in those three places, however, the proposed exemption at §__.104(e)(1) would allow for research to be exempt where sensitive identifiable private information is collected the release of which could pose some measure of risk. However, the exemption is subject to adherence to the proposed §__.105 privacy safeguards, which are designed to limit the chances that the release of that information would lead to harm. This exemption category includes research involving test development, and use of tests that have not already been shown to be valid or reliable, inasmuch as such research activity is desirable in order to determine the their validity and reliability, and the exemption category provides safeguards to ensure that results will not be used to evaluate student achievement. Note that the activities that are currently exempted under exemption category 2 (involving similar ways to collect information, but only where either the identity of the subject is not recorded or disclosure of the information would not have any adverse consequences to the subject) would be moved under the NPRM to the proposed exclusion at §__.101(b)(2)(i), rather than being under an exemption. That proposed exclusion is discussed in section II.A.2 of this preamble.

Note also that this proposed exemption would cover the research activities under the exemption in the current Rule at §__.101(b)(3)(ii), such as the research activities funded subject to the Department of Justice statute related to certificates of confidentiality (42 U.S.C. 3789g) and the

information collections subject to the confidentiality provisions of the Education Sciences Reform Act (20 U.S.C. 9573) of the Department of Education. Presumably the safeguards provided by these statutes satisfy the privacy safeguards of the proposed §__.105.

Consistent with the spirit of the principle of respect for persons, investigators should provide prospective subjects with sufficient information to make an informed decision about participation. Public comment is sought regarding whether some kind of notice must be given as a regulatory requirement for this exemption, and if so, what kind of information must be included in that notice.

The rationale for characterizing these activities as low-risk is that prospective subjects can decline to participate or answer specific questions in procedures they are already familiar with from the experiences of daily life, and, importantly, that the information will be protected through the new privacy safeguards of §__.105. The availability of this exemption is designed to reduce the volume of information collection that IRBs process, thereby enabling them to devote more time and attention to research studies which pose greater risks or involve ethical challenges.

The underlying assumptions and rationale for this exemption mirror the rationale for the exclusion proposed in §__.101(b)(2)(i)(C). Here again it is presumed that the subjects are sufficiently familiar with survey and interview procedures and educational tests to be able to knowingly and willingly provide the information, or decline to participate. The rationale for this exemption category is that prospective subjects can decline to participate or answer specific

questions in procedures they are already familiar with from the experiences of daily life, and that the information collected will be protected through the privacy safeguards of §__.105.

However, there are situations in which these assumptions would not always hold. For instance, administration of a questionnaire or participation in a focus group on a sensitive topic may induce significant stress in some individuals, or individuals approached about taking a survey may feel compelled to participate. Whether and how this exemption should be bounded so that the final rule archives a balance among the principles of beneficence, autonomy, and justice is the subject of a request for public comment on this proposed exemption. The use of this exemption is designed to enable IRBs to devote more time and attention to research studies which pose greater risks or involve more challenging ethical concerns.

5) Questions for Public Comment

45. Public comment is sought on whether the proposed exemption regarding the use of educational tests, survey procedures, interview procedures, or observation of public behavior (§__.104(e)(1)) should be applied to research involving the use of educational tests with children and whether it should also be applied to research involving the use of survey or interview procedures with children. If so, for research involving children, should the permissible survey or interview topics be limited in some way?

46. Public comment is sought on whether this exemption category should only apply to research activities in which notice is given to prospective subjects or their legally authorized

representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? Should prospective subjects be given the explicit opportunity to opt out of such research?

47. Public comment is sought on whether it is reasonable, for purposes of this exemption, to rely on the exemption determinations produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances?

48. Public comment is sought on whether this exemption category should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exemption? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.

iii. Secondary Research Use of Identifiable Private Information (NPRM at §__.104(e)(2))

1) NPRM Goal

The goal of the proposed new exemption category at §__.104(e)(2) is to facilitate secondary research using identifiable private information that has been or will be collected or generated for

non-research purposes, when prior notice has been given and privacy safeguards and prohibitions on re-use of the information are in place. Technological developments and the creation of large databases have significantly increased the potential benefits of secondary research analyses. The proposed exemption category would eliminate the need for IRB review of certain low-risk studies that only involve secondary use of identifiable private information that was collected for non-research purposes. The information would be protected under the privacy safeguards of §__.105, and respect for persons would be demonstrated through a requirement for notice. The proposed exemption is limited to the research use of the identifiable private information for the purposes of the specific research for which the investigator or recipient entity requested access to the information, not for any further secondary research use. This proposed exemption is intended to reduce IRB and investigator time and effort, and allow IRBs to focus more attention on research with higher risks or presenting other ethical challenges. The exemption would enable beneficial secondary research to occur without being impeded by administrative or IRB review, but with privacy safeguards to avoid harm and a notice requirement to show respect for persons. Public comment is sought regarding this proposal, including what limits in scope it should have, what controls and protections should be attached above and beyond the privacy safeguards of §__.105, and how best to respect the autonomy or other interests of the individuals who are the subjects of the information.

2) Current Rule

Under the current Common Rule, secondary research studies using identifiable private information undergo IRB review and approval, often using the expedited review procedure. If

the activity satisfies the relevant criteria, the IRB may waive the requirement for informed consent, which IRBs typically do.

3) ANPRM Discussion

The ANPRM proposed that with regard to an investigator's use of pre-existing data (i.e., data that were previously collected for purposes other than the currently proposed research study) originally collected for non-research purposes, then, as is currently the rule, written consent or waiver of consent would only be required if the investigator obtains information that identifies the subjects. Under the ANPRM, there would accordingly have been no change in the current ability of investigators to conduct such research using de-identified data or a limited data set, as such terms are used in the HIPAA Rules, without obtaining consent.

Second, the ANPRM proposed that if the data were originally collected for research purposes, then consent would be required regardless of whether the investigator obtains identifiers. This would have been a change with regard to the current interpretation of the Common Rule in the case where the investigator does not obtain any identifiers. That is, the allowable current practice of telling the subjects, during the initial research consent, that the information they are providing will be used for one purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented, would not have been allowed.

4) NPRM Proposal

The NPRM proposal here is for a new exemption covering the secondary research use of identifiable private information that has been or will be acquired for non-research purposes, if the following are met:

- Prior notice has been given to the individuals to whom the identifiable private information pertains that such information may be used in research;
- The privacy safeguards of §__.105 are required; and
- The identifiable private information is used only for purposes of the specific research for which the investigator or recipient entity requested access to the information.

Under the current system, IRBs frequently waive consent for research involving the secondary use of identifiable private information, particularly when the data sets are large or drawn from multiple institutions. In such circumstances, IRBs often impose privacy and data security protection requirements. However, since this proposed exemption category requires that the privacy safeguards at §__.105 are in place, requiring these studies to undergo IRB review will provide little or no additional protections to subjects, while continuing to generate potentially substantial burdens on investigators and IRBs and diverting IRB resources away from research that may involve more serious ethical challenges.

Under this proposed exemption there will be greater protections for these research subjects than is currently the case. The new privacy safeguards of §__.105 would be applied to this research, and would be the same safeguards that would be used for many other types of research under the NPRM. In addition, the scope of the exemption is limited to the specific research for which the

investigator or recipient entity requested access to the information, so the otherwise permissible uses, releases and disclosures under §__.105(c) would not apply to research covered by this exemption. Respect for persons would be given more weight insofar as the subjects would now receive notice that research might take place, which is currently not required.

Further, in many cases, other laws such as HIPAA also provide protections in the research context for the information that would be subject to this proposed exemption (e.g., clinical records), such that additional Common Rule requirements for consent may not be necessary in those contexts. Under HIPAA, these protections include, where appropriate, requirements to obtain the individual's authorization for future, secondary research uses of protected health information, or waiver of that authorization by an IRB or HIPAA Privacy Board. This proposal does not disturb those laws.

The NPRM proposal limits the use of this exemption to cases in which individuals have been informed that the information may be used in research with the goal of ensuring that research under this exemption exhibits respect for persons. In particular, by ensuring that subjects are notified that their information may be used for research, this notice requirement may enhance subject autonomy.

Alternative scopes for this provision are also proposed for consideration. A narrower scope could be envisioned that would limit the exemption to data generated by the Federal Government for which a privacy impact assessment has been conducted pursuant to section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3601 et seq, that fully describes the ways that the

information will be accessed, used, maintained, disseminated, and protected, and there is a formal written agreement between the investigator and the federal agency that requires the investigator to apply the same practices and safeguards as those addressed in the privacy impact assessment. Such a narrower interpretation might be easier to implement, and the line between §__.104(e)(2) and (f)(2) would be clearer.

Alternatively, it could be broadened to allow additional research uses of the information beyond the specific research for which the investigator or recipient entity obtained the information.

The proposed exemption category could also be revised to change the manner in which respect for persons would be demonstrated by requiring that individuals have been given the opportunity to opt out of any secondary research with their identifiable private information. This would mean that subjects could exercise their autonomy to choose not to allow their information to be used, although this would not meet the even higher standard of fully informed active consent. Under this alternative, which would give prospective subjects the opportunity to opt out, it could be argued that the balance would be struck even more in favor of respect for persons by limiting the exemption to research where more than prior notice was required. This would restrict the exemption to research where an even greater measure of respect for persons had occurred, that is, that the individuals had been given the right to decline to participate in research, rather than simply being notified that such research was going to take place. Public comment is sought regarding this alternative approach as well.

Finally, it also should be noted that section 511 of the Medicare Access and CHIP Reauthorization Act of 2015 requires the Secretary to issue a clarification or modification with respect to the application of these regulations to certain activities involving clinical data registries. This exemption category might allow certain research activities of these clinical data registries not otherwise covered by the proposed HIPAA-related exclusion at §__.101(b)(2)(iv) (i.e., when the clinical data registries are not part of a HIPAA covered entity or acting as a business associate), such as when a clinical data registry may receive information from a health care entity for research purposes.

5) Questions for Public Comment

49. Public comment is sought on the types of research that should fall under the proposed exemption. Should the proposed exemption be available to all types of research using identifiable data collected for non-research purposes or should the exemption be available only to a more limited subset of research? For example, should the proposed exemption apply only for research using records and information already subject to comprehensive privacy and other protections in other Federal laws (e.g., records held by the Federal Government subject to the Federal Privacy Act, or records governed by HIPAA or FERPA)?

Depending upon the scope of the exemption, the relationship between this exemption and the exemption proposed at §__.104(f)(2) would need to be clarified. Since a major justification for including this exemption is to reduce burden on IRBs, should the proposed exemption apply only to research for which IRBs typically waive informed consent, that is, where the research could

not practicably be carried out without a waiver of informed consent, and the rights and welfare of subjects will not be adversely affected by the waiver? Finally, is there a sufficient need for this exemption at all given the other proposed exclusions and exemptions?

50. Public comment is sought regarding whether the proposed exemption should be limited to research in which individuals had been informed of the potential future research use of their information, and given the opportunity to opt out of having their identifiable private information used for research. If the proposed exemption should be limited in this way, what information should be included in the opportunity to opt out? If the opportunity to opt out is made a condition of the exemption category how should it be structured (e.g., how long and under what circumstances should it remain in effect) and what, if any, impact should the opt out have on other provisions of the rule, such as the ability of an IRB to waive informed consent for a subsequent research study using the individual's information? Are there other or alternative mechanisms that should be required to respect individuals' autonomy and other interests?

51. Public comment is sought regarding what should constitute notice for purposes of this exemption category. Given the many different types of data that would be covered by this provision (e.g., data from private entities used for social or behavioral science research, government records for which laws already establish standards for notice, and data publicly available for harvesting from the internet), would it be possible to develop a uniform "notice" requirement? What type of notice, in terms of its dissemination and scope, should be considered to meet this requirement of the proposed exemption? With regard to the dissemination of the notice, should the notice requirement be permitted to be fulfilled through a general public notice,

not specifically directed to individuals who are potential research subjects, such as the notice allowable under the Privacy Act? Would a prominent notice posted in all clinics or other relevant public places where information will be collected be acceptable? Should each individual whose data could be used receive their own notice, such as is required of direct treatment providers covered by the HIPAA Privacy Rule? With regard to the content of the notice required by this proposed exemption, what kind of information should be included in the notice, such as the types of research that might be conducted, privacy safeguards, contact information, etc.?

52. Public comment is sought on whether, on the other hand, prior notice is necessary. Is the notice requirement proposed for this exemption a meaningful and important measure to respect individual autonomy, particularly if the notice requirement could be fulfilled through a general public posting? Current practices suggest that IRBs will frequently waive informed consent for studies involving the secondary use of identifiable private information collected for non-research purposes. If the exemption were to exclude the notice requirement, but continue to require application of the data security and privacy safeguards of §__.105 and restrict the use of identifiable private information to only purposes of the specific research for which the investigator obtained the information, would the exemption better strike a reasonable balance between respect for persons and beneficence, while eliminating the current requirement for IRB review?

53. Public comment is sought as to whether this exemption would provide appropriate protections for research conducted by clinical data registries, while enabling these research activities to proceed without delay, and what should be included in guidance regarding such

activities. Public comment is sought regarding the extent to which other exclusions or exemption categories would apply to research conducted by clinical data registries, such that the conditions of this exemption category would not apply.

d. Exemptions Subject to the Documentation Requirements of §__.104(c), the Privacy Safeguards Described in §__.105, Limited IRB Review as Described in §__.111(a)(9), and Broad Consent in Accordance with §__.116(c)

i. NPRM Goals

The goal of this proposed rule is to enable the conduct of research in the rapidly growing area of research involving biospecimens, especially genetic analyses, while recognizing the autonomy interests of people to decide whether or not to participate in this area of research. Some people have a particular interest in whether research will be carried out with their biospecimens, and want to exercise some control over their biospecimens. At the same time, biospecimen repositories are being created to enable innumerable research studies in the future, and the pace of technology development is such that the specific research studies to be carried out with those biospecimens is unknown at the time the biospecimens are collected.

ii. Current Rule

The current Rule requires IRB review and approval of research involving identifiable private information, including individually identifiable biospecimens. IRB waiver of informed consent

is allowable under the Common Rule, if the research study satisfies the criteria for waiver of informed consent. The current Rule also allows for research without consent when a biospecimen is used for research under conditions where the investigator does not possess information that would allow him or her to identify the person whose biospecimen is being studied.

iii. ANPRM Discussion

The ANPRM considered requiring written general consent for secondary research use of biospecimens originally collected in research or non-research settings regardless of whether they include identifiers. The ANPRM proposed an excused or exempt category for research involving the secondary use of biospecimens originally collected for either research or non-research purposes if there was written broad consent for the research use of the biospecimens, typically obtained at the time of the original collection. The ANPRM also considered whether the broad consent should include check-off boxes allowing subjects to consent or decline consent for types of research raising unique concerns.

iv. NPRM Proposals

The NPRM includes two exemptions proposed in §__.104(f) to facilitate storage, maintenance, and secondary research use of biospecimens and identifiable private information. Generally the exemption at §__.104(f)(1) will first be employed to allow the storage or maintenance for secondary research use of biospecimens or identifiable private information, by means of broad

consent being obtained. Following that, the secondary research that will be conducted using such biospecimens or identifiable private information could often be exempted under §__.104(f)(2).

A majority of commenters opposed the suggestion that there be consent requirements for the research use of non-identifiable biospecimens collected for purposes other than the current research study. Some commenters also favored requiring IRB review and approval for specific studies involving the use of identifiable private information and identifiable biospecimens, rather than permitting the use of a broad consent for future use to satisfy the regulatory requirement for consent. These commenters indicated that IRB review of specific research studies, and the IRB's consideration of whether a study-specific informed consent should be required or whether informed consent could be waived, was more protective of human subjects than the ANPRM recommendation permitting use of a broad consent for future use.

Commenters to the 2011 ANPRM were mostly concerned with the cost and burden that would be imposed by the requirement to obtain consent for future research use of all biospecimens, regardless of identifiability. Commenters anticipated these costs to include obtaining consent from participants and the administrative efforts required to keep track of the consent status of biospecimens. Most commenters did not provide detailed cost estimates with their comments; data are specifically requested in response to this NPRM. In addition, estimates of the type and number of studies that could not be pursued using existing samples and data because of the absence of sufficient consent are requested. Comment is also sought on the value to the public and research participants of being asked their permission for research use of their data and biospecimens.

While consideration was given to the opposition expressed by ANPRM commenters of a consent requirement for secondary research use of non-identified biospecimens, the NPRM proposes to require that consent be obtained for the research use of non-identified biospecimens, but to allow for that consent to be broad. Thus, while consent would be required for the research use of non-identified biospecimens, one would not have to obtain study-specific consent for the research use of those biospecimens, drastically reducing the burden imposed by this new requirement.

The NPRM proposal includes several protections for secondary research use of biospecimens in addition to the broad consent. Research activities falling under the exemption at §__.104(f) are subject to the requirements under proposed §__.104(c). This would require that exemption determinations be made by someone knowledgeable of the regulations, or by the to-be-created exemption determination tool (when utilized by an investigator or other individual). Additionally, the documentation requirement would allow institutions to better know the scope and volume of secondary research studies conducted at an institution. Also note that §__.104(f)(1) requires that an IRB review the consent process through which broad consent would be obtained in the non-research context, to further allay ethical concerns about obtaining broad consent in clinical and other non-research contexts.

1) Exemption for the Storage or Maintenance of Biospecimens or Identifiable Private Information for Secondary Research Use (NPRM at §__.104(f)(1))

The first exemption in this group, at proposed §__.104(f)(1), is for storage or maintenance for secondary research use of biospecimens or identifiable private information that have been or will be acquired for research studies other than for the proposed research study, or for non-research purposes, if the following criteria are met:

- Written consent for the storage, maintenance, and secondary research use of the information or biospecimens is obtained using the broad consent template that the Secretary of HHS will develop. Oral consent, if obtained during the original data collection and in accordance with the elements of broad consent outlined in §__.116(c) and (d)(3), would be satisfactory for the research use of identifiable private information initially acquired in accordance with activities excluded under §__.101(b)(2)(i) or exempt in accordance with §__.104(d)(3) or (4), or §__.104(e)(1); and
- The reviewing IRB conducts a limited IRB review of the process through which broad consent will be sought, and, in some cases, of the adequacy of the privacy safeguards described in §__.105.

This exemption category only allows for the storage or maintenance for secondary research use of biospecimens or identifiable private information. Note that this exemption does not exempt the creation of any data or the actual new collection of any biospecimens from a person through a research interaction or intervention. (For example, if the proposed research activities involved creating a research repository of DNA samples that would be obtained from people through cheek swabs, the collection of the cheek swabs would mean that the creation of the research repository would require IRB review, and would not be exempt.) This exempt category is for

secondary research use of biospecimens and identifiable private information and applies to biospecimens and identifiable private information that were initially collected for purposes other than the proposed research activity. The term 'other than the proposed activity' here means that the information or biospecimens were or will be collected for a different research study or for a non-research purpose.

In the case of a research study involving the actual new collection of biospecimens such as a clinical trial, the informed consent process could include obtaining informed consent for the original study (which study would not be exempt and would require IRB review and the usual type of consent document as required under §__.116(a) and (b)), and for secondary research use of the biospecimens. The informed consent form for the latter step (the secondary research use) could make use of the Secretary's template, in which case the biospecimen would be eligible for maintenance or storage under §__.104(f)(1) with limited IRB review or for a secondary research study under §__.104(f)(2). If the Secretary's template for broad consent is not used, the storage or maintenance for secondary research use would not meet this exemption and the consent form would need to be reviewed and approved by an IRB, either along with the IRB review of the original study, if the maintenance and storage for secondary research is known and described, or later, if it is not. Note also that if the Secretary's template is not used, the §__.104(f)(2) exemption, as discussed below, would not apply to exempt any actual secondary research studies conducted using the stored biospecimens. IRB review would be needed for each of those studies, unless the research met one of the proposed exclusions at §__.101(b)(1) or (b)(3), or the exemption found in proposed §__.104(d)(2).

This exemption requires written informed consent using the Secretary's template for broad consent for secondary research, or oral consent, in specified circumstances. This broad consent requirement will enable subjects the choice to include their biospecimens and information in this research. The consent form using the Secretary's template would include the information required in §__.116(c). Oral broad consent would also need to include all of the elements of consent at §__.116(c), and would only be permissible for the research use of identifiable private information, not biospecimens, when the identifiable private information was initially acquired as part of any of the following four excluded or exempt categories of research: (1) the exclusion related to research, not involving interventions, that involves the use of educational tests, survey procedures, interview procedures, or observation of public behavior (§__.101(b)(2)(i)); (2) the exemption related to research involving benign interventions (§__.104(d)(3)); (3) the exemption related to taste and food quality evaluation and consumer acceptance studies (§__.104(d)(4)); or (4) the exemption related to research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior (§__.104(e)(1)).

It is proposed that oral broad consent only be permitted to satisfy these exemptions regarding the secondary use of identifiable private information (§__.104(f)(1) and (f)(2)) if the identifiable private information was initially acquired as part of any of the four above-mentioned exclusion and exemption categories because these four categories are the only ones that are expected to typically involve some interaction with human subjects, and thus give investigators the opportunity to obtain oral consent from subjects for the secondary use of research data obtained as part of the initial research study.

This exemption also requires adhering to the privacy safeguards described in the proposed section §__.105.

The exemption also includes a requirement for limited IRB review (§__.111(a)(9)). The purpose of this limited IRB review is to ensure that the process of obtaining consent will occur in an appropriate way, because there may be some circumstances (for example, when someone is admitted for emergency care), when the individual is not able to make an informed considered decision. This IRB review will, for many institutions, be essentially a "one-time" event (as opposed to being needed for specific research studies); the IRB would review an overall general institutional protocol for the manner in which people can provide broad consent for the maintenance or storage of their biospecimens for future secondary research. Such a general institutional protocol would need to identify the circumstances in which broad consent would be sought for secondary research use of biospecimens so that the IRB could determine that these circumstances are consistent with the requirements for voluntary informed consent as described in the introductory language to proposed §__.116.

In addition, if there will be a change in the way the biospecimens and information will be maintained for the secondary research purposes, rather than simply changing the eligibility for secondary research status of biospecimens or information already being maintained for other purposes, then limited IRB review must also ensure that the biospecimen and information protection standards are still met. For example, if it is envisioned that the identifiable private information collected will be stored both at the institution obtaining the information, and also

stored at a second institution, an IRB would also need to determine if the §__.105 privacy safeguards are adequate.

2) Exemption for Secondary Research Use of Biospecimens or Identifiable Private Information where Broad Consent has been Sought and Obtained (NPRM at §__.104(f)(2))

The second exemption in this exemption group, at §__.104(f)(2), is for research involving the use of biospecimens or identifiable private information that have been stored or maintained for secondary research use, if consent for the storage and maintenance of the information and biospecimens was obtained as detailed using the broad consent template that the Secretary of HHS will develop. Note that oral broad consent would be allowed to the extent permitted under proposed §__.104(f)(1)(i)(A). If the investigator anticipates that individual research results will be provided to a research subject, the research may not be exempted under this provision and must be reviewed by the IRB and informed consent for the research must be obtained to the extent required by proposed §__.116(a) and (b).

This exemption category at §__.104(f)(2) is for the actual secondary research studies that will be conducted using biospecimens or identifiable private information that have been stored for unspecified secondary research studies. This exemption does not include additional analyses being conducted to support or augment the original research study for which the information or biospecimens were originally collected.

The proposed exemption category at §__.104(f)(2) requires that the privacy safeguards at §__.105 are met, and that broad consent to the earlier storage or maintenance of the biospecimens and information had already been obtained consistent with the requirements of §__.104(f)(1). This means that for secondary research using biospecimens informed consent must have been obtained using a consent form using the Secretary's template. It is presumed that research involving newborn blood spots would frequently take place using this provision.

The rationale for these two exemptions is that they provide for obtaining broad consent from subjects for the research use of specimens, honoring the principle of respect for persons, they provide protections for the information involved through the privacy safeguards of §__.105, and the limited IRB review proposed at §__.111(a)(9) ensures that the privacy safeguards and informed consent process are indeed adequate.

The exemption at §__.104(f)(2) would not apply to research in which the investigator anticipates that research results will be provided to a subject. If it is anticipated that individual research results will be returned to subjects, then the research would not meet this exemption and IRB review and approval would be required, and informed consent would need to be obtained to the extent required by §__.116(a) and (b). If the investigator does not anticipate that individual research results will be provided to a research subject as part of the research plan, but later decides to return research results to subjects, an IRB must review and approve the plan for returning these results to the subjects. It is understood that the prospective IRB review provision set forth here does not override existing law, such as the HIPAA Privacy Rule or the Federal Privacy Act, which give individuals the right to access certain information about themselves in

specified circumstances. In addition, it is recognized that clinical care needs may demand prompt reporting of findings to patients who are also human subjects, in which case it is expected that investigators would anticipate that such research results will be provided to a subject, and this exemption would not apply.

It is generally recognized that where, for example, a series of genetic analyses are performed, in a significant percentage of instances investigators will be learning information, not necessarily related to the specific purpose of their studies, that would nonetheless be significant to participants in terms of making decisions about their health care. For example, it might be learned that a woman has a gene mutation that significantly increases her risk of breast or ovarian cancer. The proposed rule does not specifically impose any obligations on investigators to provide such information to participants, so long as the consent form is clear that no such information will be given to the participants. This could have a negative impact on the current efforts to increase the willingness of people to allow their biospecimens to be used in research, if they are less inclined to provide broad consent to such research when investigators are not making any commitment to return important information that is unexpectedly learned about a participant. This could lead some investigators to decide to include in their protocols provisions for returning such results to subjects. The consequence is that such protocols will not be eligible for the proposed exemption at §__.104(f)(2), and thus would undergo full IRB review primarily for the purpose of determining what information participants should be provided regarding such "unexpected" (i.e., not related to the purpose of the research) genetic findings. In contrast, if a study only involved use of biospecimens, and no results were to be returned to subjects, no IRB

review would be required under the NPRM proposals unless IRB review is required by law (e.g., FDA-regulated devices).

At the same time, it is likely that many IRBs do not have any particular unique expertise in making these determinations about returning results, which again could lead to inappropriate variability in disclosure from study to study, and would seem to be in conflict with the ethical goal of justice.

One option that has been considered would be to create a federal panel of experts to make determinations about which unexpected findings should be disclosed to human subjects in research, and what information should be given to subjects about themselves. If this alternative proposal were adopted, then it would not be necessary to have full IRB review of these protocols. A consequence of this option would be that these types of studies could be exempt even if they proposed to return research results to subjects, so long as disclosures were made consistent with the rules announced by the federal panel. However, it is not clear that such a panel's guidance would be superior to that of IRBs.

v. Questions for Public Comment

54. Public comment is sought on whether the NPRM's proposal of exemption §__.104(f)(2) is the best option, or whether there is a better way to balance respect for persons with facilitating research.

55. Public comment is sought on whether and how the provision regarding the return of research results in the proposed exemption §__.104(f)(2) should be revised.

56. Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab, saliva).

e. Applicability of Exemptions to the Subparts (NPRM at §__.104(b); current Rule at Footnote 1)

i. Current Rule

In the current Common Rule, the application of the exemptions articulated in the current Common Rule in §__.101(b) to the subparts is specified through footnote 1 of the current Rule. It states that the exemptions do not apply to research involving prisoners, and are also limited in their application to research involving children. The current exemption at §__.101(b)(2) for research involving educational tests, survey or interview procedures or observations of public behavior does not apply to subpart D, except for research involving educational tests or observations of public behavior when the investigator does not participate in the activities being observed. The current exemptions do apply to subpart B.

ii. NPRM Proposals

While the exemptions in the NPRM are based largely on exemptions in the current Common Rule, not all of the exemptions proposed in the NPRM will apply to subparts B-D. Language at §__.104(b) explains how the proposed exemptions may be applied to the subparts. The language at §__.104(b)(1) states that all of the exemptions at §__.104 may be applied to research conducted under subpart B. Language at §__.104(b)(2) states that none of the §__.104 exemptions may be applied to research conducted under subpart C, except for research aimed at a broader population that consists mostly of non-prisoners but that incidentally includes some number of prisoners. Finally, §__.104(b)(3) states that the exemptions at §__.104(d)(1), (2), (4), §__.104(e)(2) and (f)(1) and (2) may be applied to research conducted under subpart D. The exemption at §__.104(e)(1) cannot be applied to research involving children under subpart D, because protections including IRB review and parental permission are appropriate for research involving educational tests, surveys or interview procedures, or observation of public behavior when the information collected may be individually identified and sensitive in nature.

Although this NPRM does not propose changes to the HHS regulations at 45 CFR part 46, subparts B, C and D, consideration is being given to whether the proposed exemption categories articulated in §__.104 should apply in research involving prisoners under subpart C, either if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners, as proposed in the NPRM, or if the research intends to involve prisoners as research subjects. Originally developed in 1976 by the National Commission, subpart C has at times come under scrutiny for its restrictive construction. The subpart was written in the wake of harsh criticism regarding research abuses involving prisoners that occurred or became public in the 1960s and 1970s. As a result, subpart C was written to permit research involving incarcerated

persons only if the study fits one of four categories at 45 CFR 46.306(a)(2) (an "epidemiological waiver" category was added in 2002[51]), and requires an institution to "certify" to the Secretary, HHS, before research can proceed. An additional original restriction conveyed through footnote 1 of the current Common Rule specifies that research involving prisoners may not be considered exempt under any of the current exemption categories.

Public comment is requested on whether the revised exemption categories should be permitted to apply to research involving prisoners. Considerations include the preponderance of low-risk, socio-behavioral research focused on prisoner welfare, substance abuse treatment, community reintegration, and services utilization; the occurrence of prisoner-subjects in databases or registries; and the broad interpretation of the subpart C "prisoner" definition that includes, for example, subjects in court-mandated residential substance abuse treatment.

ii. Questions for Public Comment

57. Public comment is sought on whether research involving prisoners should be permitted to apply any or all of the exemption categories found at proposed §__.104, either if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners, as proposed in the NPRM, or if the research intends to involve prisoners as research subjects.

[51] 67 FR 62432 (Oct. 7, 2002)

58. Would it be preferable for language at §__.104(b)(2) to resemble the 2002 epidemiologic waiver criteria and state that the exemptions apply except for research where prisoners are a particular focus of the research?

59. Is the proposed application of the exemptions to subparts B and D appropriate?

f. What would change in the exemptions?

- All exemption language would be found at §__.104.
- The eight proposed exemptions in §__.104 would be divided into three groupings: (1) low-risk interventions where no other requirement of the proposed rule (including informed consent and data protection) are necessary other than the determination and recording requirements (§__.104(d)); (2) research activities where the information protection measures at §__.105 must be applied (§__.104(e)); (3) secondary research involving biospecimens and identifiable private information that requires application of privacy safeguards at proposed §__.105, broad consent as discussed at proposed §__.116(c), and limited IRB review as discussed at proposed §__.111(a)(9).
- Existing exemption categories 1, 5, and 6 (current §__.101(b)(1), (5), and (6)) would be retained at §__.104(d)(1), (2), and (4). Specifically the current exemption for research on public benefit programs or demonstration projects (§__.101(b)(5) in the current Rule; §__.104(d)(2) in the NPRM) would be clarified and OHRP's guidance would be changed to include the applicability of the exemption to cover research on public benefit and service programs that an agency does not itself administer through its own employees or

agents. A requirement for publishing a list of studies under this exemption would apply for Federal agencies or departments conducting or supporting such studies.

- A new exemption would be created for certain research involving benign interventions.
- A new exemption would be created for certain research involving educational tests, survey or interview procedures, or observation of public behavior where identifiable private information was recorded so long as data protection standards are met.
- A new exemption would be created for secondary research use of identifiable private information originally collected for non-research purposes.
- A new exemption would be created for activities relating to the storage and maintenance, for secondary research use, of biospecimens and identifiable private information.
- A new exemption would be created to exempt secondary research studies that would use the biospecimens and identifiable private information stored or maintained under the above new exemption.

B. Proposed Changes to Obtaining, Waiving, and Documenting Informed Consent (§§__.116 and ___.117)

The NPRM proposals address: (1) the organization and presentation of information included in the consent document and the process to facilitate a prospective subject's decision about whether to participate in research; (2) the elements of consent, basic and additional; (3) broad consent to the storage or maintenance for secondary research use of biospecimens and identifiable private information, and the use of such stored biospecimens and information for specific research studies; and (4) attendant changes in the waiver or alteration criteria for consent.

The NPRM proposes several changes to the Common Rule with regard to the elements of informed consent and when it must be obtained (see further discussion below regarding proposed changes to the conditions for waiver of consent). In addition, it makes several new proposals that were not included in the ANPRM questions, but are offered in response to public comments received as well as internal discussions within HHS and with the other Common Rule agencies. These include the development of a Secretary's template, which will be issued in draft for public comment at a later date (the NPRM at §__.116(d)) for broad consent to the storage or maintenance for secondary research use of biospecimens, and identifiable private information and the use of such stored biospecimens and information for specific research studies. Broad consent would be permissible for the storage or maintenance for secondary research use of such information and biospecimens that were originally collected for either research studies other than the proposed research or non-research purposes. This broad consent document would meet the consent requirements for the storage or maintenance of biospecimens and identifiable private information for secondary research, as well as the use of such stored material for individual research studies.

Because biospecimens and information that have been collected for clinical use or purposes other than for the proposed research are often an important source of information and material for investigators, and the re-use of existing information and materials can be an efficient mechanism for conducting research without presenting additional physical or psychological risks to the individual, it seems prudent to consider changes to current regulations relating to those issues. Some critics, including potential and former research subjects, object to research performed on a person's biospecimens or information without consent. Conversely, investigators and patient

advocacy groups are concerned that the need for informed consent for every use of a biospecimen or data element will greatly inhibit research. They worry that obtaining individual consent for each separate research study will create unmanageable logistical demands, making valuable research impossible.

As an additional means of increasing transparency and facilitating the development of more informative informed consent forms, it is proposed that a copy of the final version of the consent form for clinical trials conducted or supported by a Common Rule department or agency would need to be posted on a publicly available Federal website. Within 60 days after the trial was closed to recruitment, the awardee or the federal department or agency conducting the clinical trial would be required to post the consent document, the name of the clinical trial and information about whom to contact for additional details about the trial.

In addition to the specific changes proposed to §__.116, comment is sought on whether Common Rule agencies should modify the definition of "legally authorized representative" (LAR). The current Rule defines LAR at §__.102(c) as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. While the NPRM proposes to retain this language, OHRP is aware that this definition has been problematic for states in which there is no applicable law permitting an LAR to consent in either a clinical or a research context. In the absence of such a law, it is almost always the case that community or other standards (such as institutional policies) define hierarchies or identify individuals who may provide legally acceptable consent, for clinical (non-research) purposes, on behalf of others who cannot consent for themselves.

However, the current regulations are interpreted to not allow such standards to constitute applicable law for purposes of the regulations, and thus such individuals are not considered legally authorized representatives for purposes of the Common Rule. Concerns that the Common Rule's current definition of LAR may be inappropriately hindering the conduct of research with subjects who lack capacity to consent have been raised by the Secretary's Advisory Committee on Human Research Protections (SACHRP)[52], the Presidential Commission for the Study of Bioethical Issues[53], and others in the research community.

Comment is therefore sought on whether a revision that would expand the current definition to also permit an LAR to be defined by an accepted common practice standard that is used in a state for determining who can legally consent to clinical care would be consistent with the ethical principles underlying the Common Rule. Such a revision would broaden the definition of LAR and permit investigators to use accepted common practice, such as an established state or local hierarchy, to allow another person to provide consent to research participation. In the absence of such a revision, it would remain the case that in certain states, there would appear to be no way (short of taking the often difficult legal step of obtaining the appointment of a legal guardian) to enroll subjects lacking decision-making capacity in research studies. Given that the current interpretation of current §__.102(c) generally is based on the proposition that the person who can legally consent on behalf of someone else for a particular clinical procedure to take place should have the authority to consent for research purposes, it could be viewed as inappropriate to

[52] Secretary's Advisory Committee on Human Research Protections. (2009, March 4). Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIIDR). Retrieved from Office for Human Research Protections: http://www.hhs.gov/ohrp/sachrp/20090715letterattach.html
[53] Presidential Commission for the Study of Bioethical Issues. (2015). Gray Matters: Topics at Intersection of Neuroscience, Ethics and Society. Retrieved from Projects: http://bioethics.gov/sites/default/files/GrayMatter_V2_508.pdf

maintain the current Rule, which produces different results in terms of when research can take place in those states that have specific laws governing such clinical consent and those that accomplish the same legal outcome through less formal regimes.

1. Required elements of informed consent (NPRM at §__.116(a), (b))

a. NPRM Goal

Many claim that consent forms have evolved to protect institutions rather than to provide potential research subjects with some of the most important pieces of information that a person would need in order to make an informed decision about whether to enroll in a research study.[54] Instead of presenting the information in a way that is most helpful to prospective subjects—such as explaining why someone might want to choose not to enroll—the forms often function as sales documents or as a means to protect against institutional liability rather than as genuine aids to good decision-making.[55] There is also a growing body of literature that suggests informed consent forms have grown too lengthy and complex, adversely affecting their ability to convey the information needed for prospective participants to make an informed decision about participating in research.[56]

[54]Levine RJ. Informed consent: Some challenges to the universal validity of the western model. *J Law Med Ethics* 1991;19(3–4):207–213.
[55] Menikoff J, Richards E. *What the Doctor Didn't Say: The Hidden Truth about Medical Research*. New York, NY: Oxford University Press; 2006:113-123.
[56] Beardsley E et al. Longer Consent Forms for Clinical Trials Compromise Patient Understanding: So Why Are They Lengthening? *Journal of Clinical Oncology*. 2007 Mar 20;25(9):e13-4.

The goal of the proposed changes to the informed consent form and process is to facilitate prospective subjects' decision about whether or not to participate in a research study, thereby enhancing autonomy.

b. Current Rule

Currently, under the Common Rule, investigators generally must ensure that the subjects' informed consent to participate in research is obtained.[57] The regulations currently require that the consent forms include at least eight specific items of information. Various aspects of the consent forms have been heavily criticized, as have the amount of time IRBs devote to editing and revising them.

c. ANPRM Discussion

The ANPRM discussed revising the regulations to provide greater specificity about how consent forms should be written and what information they should contain. The goal would be consent documents that are shorter, when appropriate, more readily understood, less confusing, that contain all of the key information in sufficient detail, and that can serve as an aid to help someone make an informed decision about whether to participate in a study.

[57] For general requirements for informed consent see §__.116 in the current Rule, and 21 CFR 50.20, .25 for FDA's comparable requirements. There are provisions under the Common Rule, that allow for the waiver of some or all of the elements of informed consent (see § __.116(c) and (d)). The Federal Food, Drug, and Cosmetic Act limits the circumstances under which informed consent can be waived. See, e.g., section 520(g) (21 U.S.C. 360j(g)) Thus, FDA regulations contain only two exceptions from informed consent under 21 CFR 50.23-24.

d. NPRM Proposals

Public comments were largely in favor of finding ways to improve consent forms. However, commenters cited several systemic concerns that could be obstacles to shortening and simplifying forms, such as regulatory, legal, and institutional requirements, and the complexity of some studies. Of those responding to questions about the causative factors, blame for making forms long and complex was shared by sponsors of clinical trials, IRBs, regulatory agencies, and institutional legal counsel. The types of information cited as contributing to the excessive lengths of forms included the requirement to describe all reasonably foreseeable research risks and the complexity of study procedures. There was no consensus on how to better explain alternatives to research participation and few comments were submitted on this topic.

Commenters offered a few suggestions for modifying or deleting the required elements of consent, such as removing boilerplate language that only protects institutions and research sponsors, as well as removing some of the required elements for minimal risk research. However, many felt that guidance, rather than regulatory change, would better improve the development of consent forms. Although many commenters noted the need for shorter and more comprehensible consent forms, most felt that the required elements of consent articulated in the Common Rule are sufficient. Commenters overwhelmingly supported the goals articulated in the ANPRM, but cautioned against an overly prescriptive or rigid approach to consent forms. However, several commenters requested guidance on what might be included in a consent form for future research use of identifiable information and identifiable biospecimens to ensure that such forms satisfied the consent requirements of the Common Rule.

A majority of commenters supported the development of regulations or guidance designed to encourage assessment of the extent to which human subjects comprehend consent forms, at least for certain types of higher risk studies or certain types of subject populations. Others argued that the regulations at §__.116 already contain language implying the need to ensure comprehension through the use of the terms "legally effective informed consent" and "language understandable to the subject."

Finally, many commenters supported making changes to HIPAA authorization requirements, as necessary, to conform to provisions of the Common Rule. In addition, most commenters were supportive of requiring investigators to disclose in consent forms certain information about the financial relationships they have with study sponsors.

To that end, the NPRM proposes adding new language to the introductory text of §__.116 to address the questions asked in the ANPRM about strengthening the informed consent requirements. It reorients the language to emphasize the need to first provide essential information that a reasonable person would want to know in order to make an informed decision about whether to participate, and to provide an opportunity to discuss that information. It requires that the information be presented in sufficient detail relating to the specific research. Furthermore, in recognition of the complaints that current consent forms are too commonly complicated documents that primarily are used to protect sponsors from legal liability, the NPRM would require (as described in the in the revised introductory language to §__.116) that the information in these forms be organized and presented in a way that did not merely provide

lists of isolated facts, but rather facilitated the prospective subject's or representative's understanding of the reasons why one might or might not want to participate. For example, for some research studies, it could be important for the discussion of the purpose of the research and the reasonably foreseeable risks of the research to be discussed together so that prospective subjects would better understand how participation in the study might alter their clinical care and ultimately, their health.

It is also proposed that in obtaining informed consent, the investigator would be required to present first the information required by this section, before providing other information, if any, to the subject. This would mean that the consent document could only include the elements of consent that were required by the rule, with any other information included in an appendix. This is intended to lead to substantially shorter consent forms, with prospective subjects receiving the most important information in the body of these relatively short forms, instead of that key information being buried in a long and overly complex document.

Public comments did not provide consensus on desirable changes to the elements of informed consent. Thus, this language aims to emphasize the necessity of addressing the basic elements of informed consent, as described in §__.116(a), in a user-friendly but sufficiently detailed manner that facilitates comprehension of the risks and potential benefits of the research. Because commenters agree that informed consent forms should be written in appropriate language, this proposal reinforces the need to include information using language understandable to the subject. This goal is consistent with Federal Plain Language guidelines and the Federal Plain Writing Act of 2010. The Secretary will publish guidance at a later time to explain how consent forms can be

written in order to comply with the requirements of this policy. It is not envisioned that the regulations would require a formal assessment to evaluate an individual's competency, but that such a practice may be appropriate for certain populations. That this ambiguity already exists in the current regulations with regard to what constitutes "legally effective informed consent" is acknowledged.

In addition, the NPRM proposes to clarify in the introductory language at §__.116 that if a HIPAA authorization is combined with a consent form, the authorization elements required by 45 CFR 164.508 must be included in the consent document and not the appendices. In other words, when consent is combined with authorization, the authorization elements should be considered to constitute one of the required elements of consent.

Since research with non-identified data does not involve "human subjects" under proposed §__.102(e), it is proposed that a new element of informed consent be required to better ensure that subjects are informed of the possibility that identifiers collected as part of a research study could be removed from the data and then used for secondary research studies without the protections provided by this policy. The new basic element of consent at §__.116(a)(9) would apply to all research collecting identifiable private information. Based on the investigator's plans, the informed consent form and process would need to inform subjects either that: (1) identifiers might be removed from the data and that the non-identified data could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the representative, if this might be a possibility; or (2) the subject's data collected as part of the research would not be used or distributed for

future research studies, even in a non-identified form. This proposed additional element of informed consent is intended to create greater transparency and enable prospective research subjects to make a more informed decision about whether to participate in research. Prospective subjects can always decline to participate in the initial research if they object to the statement provided. These changes would not apply to ongoing human subjects research in which human subjects were involved prior to the effective date of this rule.

It is anticipated that very few investigators will elect to offer the option to restrict the future research use of non-identified data, in part because of the challenges of marking and tracking such decisions. However, should they offer this option, then institutions and investigators will have to develop a system for tracking impermissible uses of non-identified information. Since most investigators will likely elect to inform subjects that identifiers might be removed from the data and distributed for future research without additional informed consent, it would be reasonable for investigators and institutions to generally assume that the secondary research use of non-identified information would be permissible unless marked otherwise.

It is possible that investigators could choose to include additional statements about their plans to use non-identified data for future research studies. For example, investigators could agree to give subjects an option about whether subjects' non-identified research data could be used for future research studies, or could agree to seek additional informed consent from subjects before using or sharing non-identified data for future research studies. However, it is anticipated that such commitments by investigators would be uncommon, and so the NPRM does not propose including such statements in the informed consent form or process. If such commitments about

the future use of non-identified information were made by investigators in the informed consent form or process, investigators would need to satisfy these commitments, which would also require the development of a tracking system.

The NPRM also proposes adding three additional elements of consent at §__.116(b)(7)-(9) that, when appropriate, would be required to be included in the informed consent form and process. These three additional elements of consent all pertain to issues that have become more relevant in recent years as science has advanced and the nature of research has changed. The proposed new element at §__.116(b)(7) would require that prospective subjects be informed that their biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit. The proposed new element at §__.116(b)(8) would require that prospective subjects be informed of whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions. The proposed new element at §__.116(b)(9) would provide subjects or their legally authorized representatives with an option to consent, or refuse to consent, to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study. Since the information that would be required to be disclosed under these three proposed additional elements of consent is often relevant to an individual's decision of whether to participate in a research study, currently such information is sometimes included in informed consent forms under the current Common Rule. The NPRM proposes to require inclusion of these additional elements, when appropriate, to better ensure that prospective subjects are more consistently provided with this information when it is information that a reasonable person would want to know in order to make an informed decision about whether to participate in a

research study. These three proposed additional elements of consent are also relevant to seeking an individual's broad consent to the storage, maintenance, and secondary research use of biospecimens or identifiable private information, so it is proposed that broad consent obtained under §__.116(c) also include these additional elements, when applicable. These clarifications and additions would have to meet the documentation requirements at §__.117(b)(1)-(2).

e. What would change?

- New language would strengthen the informed consent requirements to make sure that the most appropriate information is presented to prospective subjects in sufficient detail and in a format that is tied to understandability.
- New language would clarify that, when a HIPAA authorization is combined with consent, the HIPAA authorization elements must be part of the core elements of the consent.
- When identifiable private information is collected for research purposes, consent would be required to notify subjects if their non-identified information could be utilized for future research studies without additional consent.
- The Secretary will publish guidance in the future to explain how consent forms can be written to comply with the regulatory requirements.
- Three additional elements of consent would be required, when appropriate.

f. Question for Public Comment

60. What topics should be addressed in future guidance on improving the understandability of informed consent?

2. Broad Consent to the Storage, Maintenance and Secondary Research Use of Biospecimens and Identifiable Private Information (NPRM at §__.116(c), (d))

a. NPRM Goal

One of the primary objectives of the NPRM is to make the strength of protections commensurate with the level of risks of the research, and by so doing, reduce unnecessary administrative burdens on research. That objective has been viewed as being particularly relevant to research involving only secondary use of biospecimens and identified data, which is relatively low-risk if appropriate protections of privacy and confidentiality are in place, including protections against the misuse of biospecimens or data that could cause harm to research subjects.

b. Current Rule

The increasing use of information and biospecimens in research, often into the future and beyond the point at which an individual is directly involved in the information or biospecimen collection, requires rethinking the elements of consent in those circumstances to ensure that potential research subjects understand how their information or biospecimens might be used as well as the risks and potential benefits of such use. Critics of the existing rules have observed that the current requirements for informed consent for future research with pre-existing information and

biospecimens are confusing and consume substantial amounts of investigators' and IRBs' time and resources.

Under the current requirements of the Common Rule, if identifiers are removed, biospecimens and data that have been collected for purposes other than the proposed research can be used without any requirement for informed consent. Similarly, under the HIPAA Privacy Rule, if data are de-identified or HIPAA identifiers do not accompany biospecimens, then the Privacy Rule does not apply. When identifiers have not been removed, under the Common Rule investigators may be allowed in certain situations to obtain a consent that is broader than for a specific research study, such as for a research repository that involves obtaining biospecimens from living individuals to create a repository for future research studies. In these cases, an IRB may determine that the original consent for the creation of the research repository satisfies the requirements of the Common Rule for the conduct of the future research, provided that the elements of consent under §__.116 continue to be satisfied for the future research. Despite this existing flexibility in the Common Rule, it is believed that the current elements of consent required under §__.116 often do not continue to be satisfied for the future research.

With respect to HIPAA, HHS's prior interpretation of the HIPAA Privacy Rule was that authorizations for research needed to be study-specific, and thus, that such authorizations could not authorize certain future unspecified research. However, in January 2013, the Office for Civil Rights modified its prior interpretation.[58] Under the new interpretation, an authorization now may be obtained from an individual for uses and disclosures of protected health information for

[58] 78 FR 5611-5613 (Jan 25, 2013).

future research purposes, so long as the authorization adequately describes the future research such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for the future research purposes.

c. ANPRM Discussion

The ANPRM suggested generally requiring written consent for research use of any biospecimens collected for clinical purposes after the effective date of the new rules (such as research with excess pathological specimens). Such consent could be obtained by use of a brief standard consent form agreeing to generally permit future research. This brief consent could be broad enough to cover all biospecimens to be collected related to a particular set of encounters with an institution (e.g., hospitalization) or even to any biospecimens to be collected at any time by that institution. These studies using biospecimens collected for clinical purposes would also fall under the expanded and revised exempt categories, and thus would not require IRB review or any routine administrative or IRB review but would be subject to the data security and information protection standards. This discussed modification would conform the rules for research use of clinically collected biospecimens to the rules for biospecimens collected for research purposes. The general rule would be that a person needs to give consent, in writing, for research use of their biospecimens, though that consent need not be study-specific, and could cover open-ended future research. The ANPRM envisioned that consent could be waived in certain limited circumstances and sought comment on appropriate criteria for waiving consent.

The ANPRM suggested that this standardized broad consent form would permit the subject to say no to all future research. In addition, the ANPRM acknowledged that there are likely to be a handful of special categories of research with biospecimens that, given the unique concerns they might raise for a significant segment of the public, could be dealt with by check-off boxes allowing subjects to separately agree (or not) to that particular type of research. More specifically, the ANPRM asked whether certain flexible consent requirements could be imposed on some of these studies that would permit the use of a broad consent for future use, with a requirement that a subject's specific consent would be required before their biospecimens could be used for special categories of research.

Further, the ANPRM suggested maintaining the current prohibition that participation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using a biospecimen. With regard to the secondary research use of pre-existing data, on those occasions when oral consent was acceptable under the regulations for the initial data collection, the ANPRM envisioned that subjects would have typically provided their oral consent for future research at the time of the initial data collection; a written consent form would not have to be signed in that circumstance.

The ANPRM also noted that there would be rules that would allow for waiver of consent under specified circumstances, though those conditions would not necessarily be the same as those for other types of research.

d. NPRM Proposal

Similar to what was discussed in the 2011 ANPRM, the NPRM proposes to allow broad consent to cover the storage or maintenance for secondary research use of biospecimens and identifiable private information. Broad consent would be permissible for the storage or maintenance for secondary research of such information and biospecimens that were originally collected for either research studies other than the proposed research or non-research purposes. The broad consent document would also meet the consent requirement for the use of such stored biospecimens and information for individual research studies. As is currently the case, consent would not be required for the secondary research use of non-identified private information, such as the research use of medical records that have had all identifiers removed. The NPRM also proposes to facilitate research that uses information or biospecimens collected for purposes other than the currently proposed research by adding a new consent provision for such research at §__.116(c), which would permit individuals to provide broad consent for the storage or maintenance for secondary research use of their information and biospecimens that would not be study-specific, and would be sufficient to satisfy the consent requirement for two proposed exemptions at §__.104(f)(1) and (f)(2).

Since it is proposed that the definition of human subject be expanded to include all biospecimens, the NPRM proposes to facilitate research using biospecimens by permitting broad consent to be obtained for their storage or maintenance for secondary research. In addition, a new exemption at §__.104(f)(2) would permit the secondary research use of biospecimens without a subject being given information about the specific research study if broad consent under §__.116(c) and (d) was obtained and the privacy safeguards at §__.105 were met.

Public comments on the 2011 ANPRM revealed variable opinions on the issue of broad consent. Several commenters indicated that there is no need for additional regulations, with one university stating that it "strongly opposes more restrictive regulations about the use of these biospecimens and sees no need to change the current regulations, even or perhaps especially in the case of secondary data analysis." Other commenters opposed broad consent, stating that investigators and clinicians should obtain specific consent from individuals for each research project. This opposition was made on the ethical grounds that because individuals are not fully informed of specific research purposes for broad consent, they can never be truly informed about the use of their data. In contrast, other commenters expressed clear support for general consent for secondary research use of biospecimens and data collected during research to exempt the research from IRB review, noting that "we support the suggestion in the ANPRM to encourage general consent for the secondary research use of biospecimens and data and where this is not obtained IRB review is required." Other commenters favored requiring IRB review over permitting the use of a broad consent to approve secondary research use of identifiable data or biospecimens. These commenters believed that IRB consideration of consent requirements for individual research studies was more protective of human subjects than the ANPRM suggestions to permit broad consent for future use.

It is envisioned that the proposed broad consent provision would be used by institutions and investigators to give individuals the choice to either allow or disallow the use of their biospecimens and identifiable private information for secondary research. In some cases, institutions would be expected to seek broad consent under §__.116(c) and (d) as part of a

research protocol to create a research repository of biospecimens or information. However, in other cases it is expected that institutions, particularly institutions that do not typically conduct human subjects research, might not develop a research protocol to create a research repository, but still choose to seek broad consent from individuals for the research use of their biospecimens or identifiable private information. In such cases, these institutions might simply "tag" biospecimens and information as either available or not available for secondary research.

Since broad consent is a different form of informed consent than informed consent for a specific research study, in which individuals must be given information about a particular research study to be conducted with their biospecimens and information, the proposed requirements for broad consent under §__.116(c) and (d) would include several of the basic and additional elements of informed consent under §__.116(a) and (b), but not all, and would include several additional required elements. The proposed elements of broad consent are intended to ensure that the individual would be provided with sufficient information to make an informed decision about whether to agree to provide broad consent for a wide variety of research that may be unforeseen at the time in which consent is being sought.

The NPRM proposes to require that the broad consent describe the biospecimens and identifiable private information that would be covered by the consent, recognizing that the biospecimens and information to be used in future research studies might be collected after the consent was obtained. Broad consent for the research use of biospecimens or identifiable private information that were originally collected for a research study would generally be described in the consent document for the study that would be generating the research biospecimens or information.

Therefore, it is proposed that broad consent to the secondary research use of biospecimens and identifiable private information collected as part of a research study could cover all such research material.

However, in the non-research context, it is recognized that the biospecimens and information that the subject would be asked to permit to be stored or maintained and used for a wide range of secondary research studies would not be as readily understood as in the research context, since such non-research collections are usually less predictable or defined. Therefore, the NPRM proposes that broad consent for the research use of biospecimens or identifiable private information obtained for non-research purposes would be limited to covering either or both of the following: (1) biospecimens or identifiable private information that exist at the time at which broad consent is sought; and (2) biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained for adult subjects, and, for research involving children as subjects, biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained or until the child reaches the legal age of consent to the treatments or procedures involved in the research, whichever comes first.

The rationale for these limitations is that individuals will not know what biospecimens and information about them will be collected by an institution in the future. The 10-year time limit may make it more likely that an individual will have a better understanding of the biospecimens and information that would be covered by the broad consent, and may be a sufficiently long enough time period to appropriately facilitate secondary research using biospecimens and information. The NPRM proposes to include the standard for who is a child based upon the

definition of "children" as defined at 45 CFR §46.402(a). At the time the child became an adult, the broad consent or permission would no longer be valid and either broad consent would need to be sought from the child-turned adult, or the investigator would need to seek a waiver of informed consent in order to use the individual's biospecimens or identifiable private information for research, unless one of the exclusions or exemptions were applicable.

The Common Rule departments and agencies contemplated proposing that the scope of broad consent to secondary research use of individually identifiable clinical information or biospecimens that were originally collected for non-research purposes would be limited to (1) clinical information and biospecimens already existing at the institution at the time broad consent was sought, and (2) clinical information and biospecimens collected as part of an identified clinical encounter. Although it was recognized that this limitation related to an identified clinical encounter would give individuals more meaningful information about the scope of future clinical information and biospecimens that would be covered by their broad consent, it was determined that limiting the scope of the broad consent in this manner would be very difficult to implement and would require rigorous tracking on an individual-subject basis. Therefore, this proposal was not included in the NPRM, and was instead replaced with the above proposal that uses a limitation based on a period of years.

In addition, the Common Rule departments and agencies contemplated proposing that for nonclinical information collected for non-research purposes (e.g., education and court records, financial records, military records, employee records, or motor vehicle records), broad consent would only be required to include a clear description of the types of records or information that

were or will be collected and the period of time or event during which information collection may occur. However, it was decided that all biospecimens and identifiable private information originally collected for non-research purposes should be bound by the same limitations, regardless of whether the materials were originally collected for clinical or nonclinical purposes.

The proposed element of broad consent, at (§__.116(c)(1)(iv)), includes a requirement that subjects be informed that they may withdraw consent, if feasible, for research use or distribution of the subject's information or biospecimens at any time without penalty or loss of benefits to which the subject is otherwise entitled. Information that has been stripped of identifiers might not be traceable. Thus, it might not be feasible to withdraw consent for future use or distribution in this case. If, however, an investigator committed to permitting a subject to discontinue the use of such information, it is expected that the investigator would honor this commitment by not stripping identifiers. The regulations would not require investigators to make such a commitment.

Another of the proposed elements of broad consent, at (§__.116(c)(1)(viii)), relates to the public posting of non-identifiable data about a subject. This proposed element of broad consent would include an option, when relevant, for an adult subject or the subject's legally authorized representative to consent or refuse to consent, to the inclusion of the subject's data, with removal of the identifiers listed in the HIPAA Privacy Rule at 45 CFR 164.514(b)(2)(i)(A) through (Q), in a database that is publicly available and openly accessible to anyone. This provision is being proposed in the context of increasing interest in inviting study participants to allow their study data, in some cases including genomic data, to be made publicly available in order to maximize

the potential for research that spurs increased understanding of disease processes. Under this provision, the consent document would be required to prominently note the option for the participant to allow the investigator to publically post (e.g., on a website) the participant's genomic or other potentially identifiable sensitive information, and to include a description of the risks associated with public access to the data.

To facilitate the use of broad consent, the NPRM proposes that the Secretary of HHS will publish in the Federal Register templates for broad consent that would contain all of the required elements of consent in these situations. It is envisioned that there would be at least two broad consent templates developed: one for information and biospecimens originally collected in the research context, and another for information and biospecimens originally collected in the non-research context.

In addition, two exemptions are proposed related to facilitating secondary research use of biospecimens and identifiable private information when the Secretary's broad consent template is used. These exemptions are described in section II.A.3 of this preamble.

The NPRM also proposes that the template for consent established by the Secretary may serve as the written consent form in circumstances when the proposed exemption categories at §__.104(f) require written consent. In circumstances where §__.104(f)(1) allows for oral consent, a subject's oral consent for secondary research use of identifiable private information must be documented such that the consent is associated with the subject's identifiable information. If this requirement

is met through the use of written documentation, the subject would not be required to sign anything.

e. What would change?

- No change would be made in the current regulatory framework allowing research use of non-identified private information without consent, except that, when relevant, individuals would be given an option to consent or refuse to consent to the inclusion of their data, with the removal of certain identifiers, in a publicly available database.
- Broad consent would be permissible for the storage or maintenance for secondary research use of biospecimens and identifiable private information, and for the use of such stored material for individual research studies.
- No change would be made to the definition of "legally authorized representative."

f. Questions for Public Comment

61. Public comment is sought on whether broad consent to secondary research use of information and biospecimens collected for non-research purposes should be permissible without a boundary, or whether there should be a time limitation or some other type of limitation on information and biospecimens collected in the future that could be included in the broad consent as proposed in the NPRM. If a time limit should be required, is the NPRM proposal of up to 10 years a reasonable limitation? Would a limitation related to an identified clinical encounter better inform

individuals of the clinical information and biospecimens that would be covered by a broad consent document?

62. Public comment is sought on whether all of the elements of consent proposed at §__.116(c) should be required for the secondary use of biospecimens or identifiable private information originally collected as part of a research study that was conducted without consent because either the original research study met an exclusion or exempt category of research, or a waiver of consent was approved by an IRB.

63. Public comment is sought on whether oral consent should be permissible in limited circumstances as proposed under exemption §__.104(f)(1).

64. Would research subjects continue to be appropriately protected if the definition of "legally authorized representative" were broadened to include individuals authorized by accepted common practice to consent on behalf of another individual to participation in clinical procedures? If the definition of "legally authorized representative" was broadened in this way, public comment is sought on the interpretation of "accepted" and "common" as these terms would be used in the revised definition.

3. Waiver of Informed Consent or Documentation of Informed Consent (NPRM at §§__.116(e), (f) and __.117)

a. NPRM Goals

The goals of the proposals related to the waiver of informed consent and the documentation of informed consent are to uphold individuals' autonomy interests in determining whether their biospecimens and identifiable private information may be used for secondary research, to facilitate the recruitment of prospective research subjects, and to create more flexible rules for documenting informed consent for certain subject populations.

b. Current Rule

Currently the Common Rule permits an IRB to waive the requirements for obtaining informed consent under two sets of circumstances described at §__.116(c) or (d)). The most common set of circumstances requires that four specific criteria be satisfied (§__.116(d)).

Under the current Common Rule at §__.117(c), IRBs may waive the requirement for the investigator to obtain a signed consent form for some or all subjects. The current criteria for such a waiver may not be flexible enough for dealing with a variety of circumstances, such as when federally sponsored research is conducted in an international setting where for cultural or historical reasons signing documents may be viewed as offensive and problematic.

c. ANPRM Discussion

The ANPRM asked whether changes to the regulations would clarify the current four criteria for waiver of informed consent and facilitate their consistent application. The ANPRM also asked

for comments on the information investigators should be required to provide to prospective subjects in circumstances where the regulations would permit oral consent. Additional questions focused on whether there are additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent, and whether there are types of research in which oral consent without documentation should not be permitted.

d. NPRM Proposals

Many commentators have argued that these conditions for waiver of consent are vague and applied haphazardly at different institutions.[59, 60] In response to these concerns, SACHRP, through its Subcommittee on Subpart A, developed several recommendations regarding the interpretation of these waiver criteria.[61] In particular, commenters have questioned the meaning of the criterion at §__.116(d)(2) that the waiver or alteration will not adversely affect the rights and welfare of the subjects. Questions have also been raised about the meaning of the term "practicably" as used in §__.116(d)(3), which states that the research could not practicably be carried out without the waiver or alteration.

Further, some have argued that the requirements for obtaining waivers of informed consent or waivers of documentation of informed consent are confusing and inflexible, which leads to

[59] Green LA, Lowery JC, Kowalski CP, Wyszewianski L. Impact of institutional review board practice variation on observational health services research. *Health Serv Res* 2006;41:214-230.
[60] Sanders AB, Hiller K, Duldner J. Researchers' understanding of the federal guidelines for waiver of and exception from informed consent. *Acad Emerg Med* 2005;12:1045-1049.
[61] Secretary's Advisory Committee on Human Research Protections (2008, January 31). SACHRP Letter to HHS Secretary. Retrieved from Advisory Committee (SACHRP): http://www.hhs.gov/ohrp/sachrp/sachrpletter013108.html .

inconsistent application.[62] These problems may not be inherent in the language of the Common Rule, but there may be some changes to the regulations or clarifications as to how to interpret and implement such regulations that could improve informed consent forms and the informed consent process.

The NPRM offers several proposals related to the waiver or alteration of informed consent provisions (§__.116(c) and (d) in the current rule, §__.116(e) and (f) in the NPRM). The NPRM proposes at §__.116(f)(1)(iv) to retain the language found in §__.116(d)(2) of the current Rule regarding the necessity to evaluate the rights and welfare of subjects before issuing a waiver of consent or altering consent procedures. Despite the vagueness of the term, IRBs should consider whether there are considerations distinct from the risk of harm and discomfort that the IRB should be able to take into account in deciding whether to approve a waiver or alteration of informed consent. Note that SACHRP's recommendations included a comment that the IRB should determine "…that the waiver or alteration does not adversely impact the ethical nature or scientific rigor of the research…," which implies that there could be ethical considerations other than the degree of risk that could legitimately affect the IRB's decision.

This criterion can be interpreted to include rights conferred by pertinent federal law or regulation, relevant state or local law, the stipulations at §__.101(e) and (f) (in both the NPRM and the current Rule), or laws in other countries where research is to be conducted. It could also include considerations of privacy or the right to decide how someone is going to be treated, where the IRB determines that subjects have such a right that the waiver would adversely impact,

[62] *See supra* note 59.

or where the waiver would preclude them from obtaining a benefit they would otherwise receive. We recognize that further guidance regarding this criterion would be helpful.

HHS has also evaluated the utility of the term "practicably" contained in the elements of waiver or alteration of consent (§__.116(d)(3) in the current Rule). The NPRM proposes to keep this terminology at §__.116(f)(1)(ii) in the NPRM. SACHRP has noted that the commonly accepted definitions of the term "practicably" are (1) feasible; (2) capable of being effected, done or put into practice; and (3) that may be practiced or performed; capable of being done or accomplished with available means or resources. SACHRP emphasized this criterion states that the research could not practicably be carried out without the waiver or alteration. In other words, it would not be practicable to perform the research (as it has been defined in the protocol by its specific aims and objectives) if consent was required. Thus it is impracticable to perform the research, and not just impracticable to obtain consent. SACHRP also offered the following concepts to help an IRB determine whether the research could not be practicably carried out without the waiver of consent: (1) scientific validity would be compromised if consent was required; (2) ethical concerns would be raised if consent were required; (3) there is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained; (4) practicability should not be determined solely by considerations of convenience, cost, or speed.[63]

[63] See Secretary's Advisory Committee on Human Research Protections (2008, January 31). SACHRP Letter to HHS Secretary. Retrieved from Advisory Committee (SACHRP): http://www.hhs.gov/ohrp/sachrp/sachrpletter013108.html.

SACHRP's recommendations are consistent with OHRP's interpretation of this waiver criterion. Consideration was given to replacing the term practicably with another term such as feasibly, but HHS is uncertain whether such a change would improve the understanding of this criterion. Thus the NPRM proposes to retain this phrase.

Few comments to the 2011 ANPRM were received on this topic although many commenters expressed support for clarifying the key terms through guidance or altering the criteria. In particular, most comments on this topic noted the confusion that IRBs face when trying to understand the meaning of the terms "practicably" and "adversely affect the rights and welfare of subjects." Some commenters expressed the opinion that the waiver criterion concerning rights and welfare should be interpreted to include reference to rights conferred by other federal laws or regulations, state or local laws, or laws in other countries where research is to be conducted. Some comments reflected concerns about privacy or security. Several commenters also pointed to the need to consider community norms throughout the consent process, including its documentation.

The NPRM proposes to add a new waiver criterion at §__.116(f)(1)(iii), which would require that, for research involving access to or use of identifiable biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers. This criterion was modeled on the comparable criterion in the HIPAA Privacy Rule, which requires that the research could not practicably be conducted without access to and use of the protected health information. The principle embodied in this additional criterion is that non-

identified information should be used whenever possible in order to respect subjects' interests in protecting the confidentiality of their data and biospecimens.

Additional more stringent waiver conditions apply to research involving biospecimens, specifically that (1) there are compelling scientific reasons for the research use of the biospecimens; and (2) the research could not be conducted with other biospecimens for which informed consent was or could be obtained. Under this new, more stringent waiver standard, the circumstances in which a waiver could be granted by an IRB should be extremely rare.

The Common Rule departments and agencies considered whether to require institutions or IRBs to report to OHRP when this waiver of consent for research involving the use of biospecimens was approved by an IRB. If such a reporting were required, it is envisioned that OHRP could use the information to consider whether the waiver provision was being implemented appropriately or whether regulatory changes might be needed (e.g., because such waivers were too frequently being granted). It is estimated that such a reporting requirement would constitute almost no burden to institutions, since the very premise behind the waiver provision is that such waivers should be extremely rare. It is also recognized that such a reporting requirement might deter IRBs from utilizing the waiver provision. The NPRM does not include a reporting requirement to OHRP when this waiver of consent is approved by an IRB, but public comments are requested on whether such a reporting requirement should be included in the final rule.

The Common Rule departments and agencies also considered whether the NPRM should propose that a waiver of consent not be permissible for secondary research involving the use of

biospecimens. The purpose of such a requirement would be to encourage investigators to seek broad consent for such research. This proposal was not included in the NPRM, but public comments are requested on whether such a prohibition to waive informed consent should be included in the final rule.

In addition, the NPRM proposes that the Common Rule prohibit IRBs from waiving informed consent if individuals were asked and refused to provide broad consent to the storage and maintenance for secondary research use of biospecimens and identifiable private information. If a subject refused to provide broad consent, it is proposed that this refusal would need to be recorded by the investigator to better ensure that the subject's wishes would be honored.

The proposal to not allow any waivers of consent by an IRB with regard to the secondary research use of identifiable private information if an individual was asked to consent to such use, and refused to consent, was thoroughly considered during the drafting of this document. On the one hand, a core initial motivation for this NPRM has been the recognition that we should not be imposing unnecessary burdens on low-risk research that is capable of producing important knowledge. Re-using data that has been generated for other purposes, when appropriate protections for privacy and confidentiality are in place, seems to fit within that category. Moreover, with society's growing abilities to rapidly generate massive data sets, and manipulate such data using cutting-edge algorithms, research using "big data" seems more important than ever. At the same time, however, it is recognized that if an individual is asked to provide consent and declines or refuses to do so, the individual's choice should be honored, except perhaps under only very rare circumstances that justify overriding an individual's autonomy interest.

Most of the provisions in this NPRM regarding the research use of identifiable private information have led to the conclusion that, when there are appropriate privacy protections in place, the balance between respect for persons and beneficence should come out in favor of facilitating the research, including not requiring informed consent in many instances. In recognition of this circumstance, while the NPRM proposes new consent requirements related to biospecimens (justified primarily by the special autonomy interest of a person in controlling the research use of such biospecimens), it does not impose such consent requirements with regard to research use of a person's identifiable private information. Accordingly, in most respects, the current Rules—which do allow such use without consent, provided that an IRB has reviewed the study and found that it meets the criteria for the waiver of consent—are retained with regard to the secondary research use of such information. For research involving the secondary use of identifiable private information, waivers of consent appear to currently be quite frequently given by IRBs, and represent a significant (and likely growing) portion of the research universe.

Accordingly, even after the implementation of this NPRM, an individual will still generally not have the right to prevent secondary research taking place using their identifiable private information, in the event that an IRB approves a waiver of consent for such a study. (Indeed, this is only one of the circumstances in which the NPRM allows such research to take place without consent; the NPRM has actually expanded such circumstances through some of the exclusions and exemptions, based on the ethical analysis mentioned above.) The main alteration of this rule by the NPRM would be in the circumstance described above: where the individual happened to

be asked to sign a broad consent regarding the use of that information, and they refused to do so. If that happened, an IRB would no longer be able to waive consent.

This is a complicated issue, and as discussed below, comments are sought on various aspects of the proposal to allow for broad consent for secondary use of identifiable private information, including whether it is appropriate to include the limitation on an IRB's ability to waive consent where a person has been asked to sign a broad consent form, but refused.

The NPRM also clarifies that waivers of informed consent and the waivers related to documenting informed consent might not be permitted for research subject to FDA regulation. For example, research conducted with a waiver of informed consent, or its documentation, may, if submitted in support of a marketing application to FDA, become subject to certain applicable informed consent requirements under 21 CFR part 50.

A provision has also been added at §__.116(g) in the NPRM to address concerns that the current regulations require an IRB to determine that informed consent can be waived under the current §__.116(d) (§__.116 (e) and (f) in the NPRM) before investigators may record identifiable private information for the purpose of identifying and contacting prospective subjects for a research study. This requirement to waive informed consent is viewed as burdensome and unnecessary to protect subjects, and is not consistent with FDA's regulations, which do not require informed consent or a waiver of informed consent for such activities. This proposal in the NPRM is intended to address these concerns and to make the Common Rule consistent with the

FDA's regulations by eliminating the requirement for the IRB to waive informed consent for these activities while explicitly assuring that the information will be protected.

With regard to documentation requirements, the NPRM proposes to alter the language at §__.117(b)(1) to specify that the consent document should include only the language required by §__.116, with appendices included to cover any additional information. The goal here is to reduce the length and complexity of the document and to ensure that the elements of information essential to decision-making receive priority by appearing in the main document.

In addition, the NPRM would make it explicit in the regulatory language at proposed §__.117(c)(1)(iii) that if the subjects are members of a distinct cultural group or community for whom signing documents is not the norm, so long as the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained, the requirement to obtain a signed consent form may be waived. Documentation must include a description as to why signing forms is not the norm for the distinct cultural group or community.

Finally, as discussed above, to facilitate tracking of broad consent to storage or maintenance for secondary research use of biospecimens or identifiable private information, and to provide information to IRBs should IRB review be required, waiver of documentation of consent for the research use of such biospecimens would not be allowed based upon a new provision at §__.117(c)(3). The regulatory language proposed at §__.117(c)(4) would also clarify that waivers of documentation may not be permitted for research subject to regulation by FDA.

e. What would change?

- A new waiver criterion would be added at §__.116(f)(1)(iii) requiring that, for research involving access to or use of biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers.
- Additional waiver criteria would apply to research involving the use of biospecimens.
- If a person was asked to provide broad consent to store or maintain for secondary research use biospecimens or identifiable private information and refused to do so, a waiver of consent would not be allowed with respect to the research use of such person's biospecimens or private identifiable information.
- A new provision would be added at §__.116(g) stating that an IRB may approve a research proposal in which investigators obtain identifiable private information without individuals' informed consent for the purpose of screening, recruiting, or determining the eligibility of prospective human subjects of research, through oral or written communication or by accessing records, in order to obtain informed consent, if the research proposal includes an assurance that the investigator will implement standards for protecting the information obtained in accordance with and to the extent required by §__.105.
- The language at §__.117(b)(1) would be altered to specify that the consent document should include only the language required by §__.116, with appendices included to cover any additional information. The goal here is to reduce the length and complexity of the

document and to ensure that the elements of information essential to decision-making receive priority by appearing in the consent document.

- A new provision would be added at §__.117(c)(1)(iii) allowing a waiver of the requirement for a signed consent form if the subjects are members of a distinct cultural group or community for whom signing documents is not the norm. This would be allowed only if the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative method for documenting that informed consent was obtained.

f. Questions for Public Comment

65. Public comment is sought on how the waiver criterion regarding "practicably" at §__.116(d)(3) could be explicitly defined or otherwise clarified (e.g., what term should replace "practicably"?).

66. Public comment is sought on the proposed differences between the criteria for waiving informed consent for the research use of biospecimens versus identifiable information.

67. Public comment is sought on whether the proposal to permit an IRB to waive consent for research involving the use of biospecimens should be included in the regulations.

68. Public comment is sought on the proposal to permit an IRB to waive consent for the secondary use of biospecimens or information originally collected for *research* purposes, even if the original research study required subjects' informed consent.

69. Public comment is sought regarding how likely investigators are to seek broad consent for the use of identifiable private information (as contrasted with biospecimens), given that there are provisions within the NPRM that would make it easier to do such research without consent (such as the new exemption at §__.104(e)(2)). In this regard, note that the NPRM proposal to prohibit waiver of consent by an IRB if a person has been asked for broad consent and refused to provide it might create a disincentive on the part of investigators from choosing to seek broad consent for research involving secondary use of identifiable private information. Given the costs and time and effort involved in implementing the system for obtaining broad consent for the use of identifiable private information and tracking when people provide consent or refuse to do so, are the benefits to the system likely to outweigh the costs, and if so, should the broad consent provisions be limited to obtaining broad consent for research use of biospecimens?

70. Public comment is sought on the proposed prohibition on waiving consent when an individual has been asked to provide broad consent under §__.116(c) and refused. In particular, how would this prohibition on waiving consent affect the secondary research use of identifiable private information? If an individual was asked to provide such consent, should the absence of a signed secondary use consent be considered a refusal? Does this prohibition on waiving consent for the secondary use of identifiable private information create a disincentive for institutions to seek broad secondary use consent and instead seek a waiver of consent from an IRB? Under

what circumstances, if any, would it be justified to permit an IRB to waive consent even if an individual declined or refused to consent?

4. Posting of Consent Forms

a. NPRM Goals

Public posting of consent forms is intended to increase transparency, enhance confidence in the research enterprise, increase accountability, and inform the development of future consent forms.

b. NPRM Proposal

Thus, the NPRM proposes a new provision at §__.116(h)(1) that would require that a copy of the final version of the consent form (absent any signatures) for each clinical trial conducted or supported by a Common Rule department or agency be posted on a publicly available federal website that will be established as a repository for such consent forms. The name of the protocol and contact information would be required to be included with the submission of the consent form. The primary purpose of this provision is to improve the quality of consent forms in federally funded research by assuring that—contrary to current practices, under which it is often very difficult to ever obtain a copy of these documents—they eventually would become subject to public scrutiny. It is anticipated that the website will be searchable.

Under proposed §__.116(h)(2), the consent form must be published on the website within 60 days after the trial is closed for recruitment. By final consent form, it is anticipated that investigators generally will post the version of the consent form that had been most recently approved by an IRB. Note that even though a newer consent form could be developed after the timeframe specified here, investigators would only be required to post one consent form. Thus, even if a modification to a consent form occurs after it has been posted, investigators would not be required to re-post an updated document. Moreover, only one posting would be required for each multi-site study. There is no expectation that a version would need to be posted for each study site.

A website would be developed by HHS, which could be used by other Federal departments or agencies, or the other Federal departments or agencies could create their own websites for the posting of these consent forms.

c. What would change?

- A new provision at §__.116(h) would require that, for clinical trials conducted or supported by a Common Rule department or agency, a copy of the final version of a consent form would have to be posted on a publicly available federal website within 60 days after the trial is closed for recruitment.

C. Proposed Changes to Protect Information and Biospecimens (NPRM at §__.105)

1. NPRM Goal

IRBs were not designed to evaluate risks to privacy and confidentiality, and often have little expertise in these matters. Setting uniform specific standards will help to assure appropriate privacy and confidentiality protections to all subjects, without the administrative burden of needing a specific committee review of the privacy and confidentiality protections of each study.

Increasing research use of genetic information, information obtained from biospecimens, and the ability to more easily merge multiple sources of administrative and survey datasets (e.g., medical records, claims data, vital records, and information about lifestyle behaviors from surveys) have increased the stakes associated with data breaches. For example, the unauthorized release or use of information about subjects such as the disclosure of Social Security or Medicare numbers may pose financial risks, and disclosure of illegal behavior, substance abuse, or chronic illness might jeopardize subjects' current or future employment, or cause emotional or social harm. The risks of a large portion of social and behavioral research are also generally informational risks.

The goal of the NPRM here is to create information privacy protections that would apply to research, calibrated to the level of identifiability and sensitivity of the information being collected.

2. Current Rule and Other Regulatory or Statutory Requirements

Currently, the Common Rule at §__.111(a)(7) requires that IRBs evaluate each study with regard to all levels of risk and are expected to determine whether the privacy of subjects and the confidentiality of their information are protected. Under the Common Rule, IRBs must review each individual study's protection plan to determine whether it is adequate with respect to the informational risks of that study.

In addition, the HIPAA Privacy Rule addresses some of these informational risks by imposing restrictions on how individually identifiable health information collected by health plans, health care clearinghouses, and most health care providers ("covered entities") may be used and disclosed, including for research. In addition, the HIPAA Security Rule (45 CFR Parts 160 and 164, Subparts A and C) requires that these entities implement certain administrative, physical, and technical safeguards to protect this information when in electronic form from unauthorized use or disclosure. However, the HIPAA Rules apply only to covered entities (and in certain respects to their business associates), and not all investigators are part of a covered entity. Moreover, the Privacy Rule does not apply specifically to biospecimens in and of themselves.

Separate from the HIPAA Rules, the Privacy Act of 1974, as amended (5 U.S.C. 552a) requires Federal agencies to protect certain information in their possession and control. However, it does not apply to non-Federal investigators.

3. ANPRM Discussion

The ANPRM suggested establishment of mandatory data security and information protection standards for all studies that involve the collection, generation, storage, or use of identifiable or potentially identifiable information that might exist electronically or in paper form or contained in a biospecimen. It put forward the idea that these standards might be modeled after certain standards of the HIPAA Rules and asked a series of questions about how best to protect private information.

4. NPRM Proposals

Some public comments reflected confusion about the focus of the suggested standards and whether they would apply to information or biospecimens that were not individually identifiable. Although most commenters confirmed the need to protect the privacy and confidentiality of information of human subjects in research, a majority expressed serious concerns about the merits of requiring all investigators to meet standards modeled on certain HIPAA standards, such as those in the HIPAA Security Rule. Most commenters expressed the opinion that certain HIPAA standards are not well suited to some research of various kinds carried out by investigators not subject to the HIPAA Rules. Some commenters claimed that the HIPAA privacy safeguards do not adequately protect individuals' information. Many commenters claimed that standards modeled after certain HIPAA standards would be unnecessarily burdensome for studies in the behavioral and social sciences where the data are often less sensitive than health information.

Some comments maintained that HIPAA-like standards would not always be suitable for the variety of research methods and procedures for the collection and storage of information in research activities not subject to the HIPAA Rules. Some commented that certain HIPAA standards would not be suitable because of the location of the research activity, or because the kind of institution supporting the research was significantly different from a covered entity. Others thought the HIPAA standards create confusion and complications for investigators and institutions that would increase if standards modeled on certain HIPAA standards were applied across the board. At the same time, regardless of the specific standards to be employed under this approach, several commenters noted that the additional administrative burden that might be created by establishing a data security and information protection system could be offset by the decreased time and attention IRBs would have to invest in reviewing every study that required data or biospecimen protections. They also noted that many institutions already have required data and biospecimen protection systems in place.

Some commenters noted that expansion of some of the exemption categories could only be ethically acceptable if those research activities were subject to a requirement for data security and information protection, because information collected for some research studies would no longer be collected under a research plan approved by an IRB. With regard to an absolute prohibition against re-identifying de-identified data, many commenters expressed concern, and provided reasons why re-identification might be valid or even desirable, including the need to return clinically relevant research results to an individual. For example, if the research uncovers information that might have important clinical significance for an individual, re-identification could be used so that the individual could get care. In addition, they pointed out that the current

Common Rule requires investigators who re-identify non-identified private information as part of a research study to comply with the current Common Rule regulatory requirements.

The NPRM proposes to require that investigators and institutions conducting research subject to the Common Rule implement reasonable safeguards for protecting against risks to the security or integrity of biospecimens or identifiable private information. Given the significant concerns of public commenters about the idea discussed in the ANPRM of adopting the standards solely modeled on certain standards of the HIPAA Rules, the NPRM proposes several sets of standards, and allows a choice about which to use. First, the NPRM proposes to have the Secretary of HHS publish a list of specific measures that an institution or investigator can use to meet the requirements. The list would be evaluated and amended, as appropriate, after consultation with other Common Rule departments and agencies. The proposed list will be published in the Federal Register, and public comment on the proposed list will be sought before the list is finalized.

The list of specific safeguards that would be identified by the Secretary will be designed such that they could be readily implemented by the individual investigator, could build on existing safeguards already in place to protect research data, and would involve minimal cost and effort to implement. These standards would include security safeguards to assure that access to physical biospecimens or data is limited only to those who need access for research purposes. These standards would also assure that access to electronic information is only authorized for appropriate use. Finally, these safeguards would assure that information and biospecimens posing informational risks to subjects would be protected according to appropriate standards.

Second, if an institution or investigator is currently required to comply with the HIPAA rules, then the safeguards required by the Common Rule would be satisfied. No additional requirements are proposed to protect information that is subject to the HIPAA Rules. The NPRM also proposes to clarify at §__.105(d) that the provisions at §__.105 do not amend or repeal the requirements of 45 CFR parts 160 and 164 for the institutions or investigators to which these regulations apply pursuant to 45 CFR 160.102. Institutions or investigators that are not required to follow HIPAA could voluntarily implement the HIPAA Rules and be considered to satisfy the §__.105 privacy protections requirements. For Federal departments and agencies that conduct research activities that are or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and the research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq, the requirements of §__.105 will be deemed satisfied.

For the purposes of informing the development of the §__.105 privacy safeguards, comment is sought on what types of safeguards would be appropriate.

There are additional statutes or acts that mandate the protection of privacy and confidentiality of identifiable private information that may be reasonable to include in §__.105(b) as additional standards which, if research is already subject to those standards or a voluntarily election to

comply with them is made, should perhaps be viewed as meeting the new requirement. These include:

- The Confidential Information Protection and Statistical Efficiency Act, 44 U.S.C. 3501 note;
- The Family Educational Rights and Privacy Act of 1974, 20 U.S.C. 1232g;
- The Census Act, 13 U.S.C. 1 et seq.;
- Agency for Healthcare Research & Quality (AHRQ) statutory provision protecting the confidentiality of identifiable data obtained for research purposes by AHRQ or its contractors and grantees, 42 U.S.C. 299c-3(c);
- The CDC National Center for Health Statistics (NCHS) statutory confidentiality provision at Section 308(d) of the Public Health Service Act, 42 U.S.C. 242m(d) (using nearly identical language to the AHRQ statutory provision referenced above);
- The Substance Abuse and Mental Health Services Administration authorizing statute regarding confidentiality of alcohol and drug abuse patient records at 42 U.S.C. 290dd-2;
- The Department of Justice statute related to confidentiality of information used by the Office of Justice Programs at 42 U.S.C. 3789g;
- The Department of Education statute related to Education Sciences Reform at 20 U.S.C. 9573.

Public comment is sought on whether any of the above referenced statutes or acts would serve the goals of §__.105. Note that the statutes and acts referenced in §__.105(b) are currently referenced in the proposed exclusions at §__.101(b)(2)(i) (exclusion for surveys, educational

tests, and public observation) and §__.101(b)(2)(iii) (exclusion for federal departments or agencies to use pre-existing federally generated non-research data). To that end, public comment is also sought as to whether the goals of the NPRM are served by referencing any of the aforementioned statutes, acts, or standards in the exclusions proposed in §__.101(b)(2)(i) and (iii).

In order to reduce burden on IRBs that may under the current regulation be tasked with ensuring that safeguards are commensurate with informational risk, IRB review of required safeguards generally would not be required. Note that while the proposed language at §__.111(a)(7) requires that IRBs consider if the privacy safeguards at §__.105 are sufficient to protect the privacy of subjects and the confidentiality of data, the presumption would be that these privacy safeguards are sufficient in most circumstances.

The new section includes conditions for use and disclosure of research information to other entities, consistent with those protections to participants in research conducted by Federal employees and their contractors. It requires that protections be in place when biospecimens or identifiable private information are shared for appropriate research or other purposes as specified in the rule. Unless required by law, the NPRM would limit the re-disclosure of biospecimens and identifiable private information that were obtained for research purposes to the following four purposes: (1) for human subjects research regulated under the Common Rule; (2) for public health purposes; (3) for any lawful purpose with the consent of the subject; or (4) for other research purposes if the institution or investigator has obtained adequate assurances that: the recipient investigator will implement and maintain the level of safeguards required by this

provision, and the research has been approved by an IRB under §__.111 (except for human subjects research that qualifies for exclusion under proposed §__.101(b) or exemption under proposed §__.104 and the recipient will not further disclose the biospecimens or identifiable private information except as permitted by this provision (NPRM at § __.105(c)).

These four purposes are additional uses or disclosures of biospecimens or identifiable private information collected in research, because the subjects themselves consented, or because the information and biospecimens will continue to be safeguarded, or because the public health will be served. For the purposes of this requirement, an institution or investigator must obtain adequate assurances through the use of a written agreement with the recipient of the biospecimens or identifiable private information that the recipient will abide by these conditions. In developing this provision, Common Rule departments and agencies discussed whether it was appropriate to limit the re-disclosure of biospecimens and identifiable private information "unless [such a disclosure was] required by law" or if some other standard (such as "unless [such a disclosure was] authorized by law") would be appropriate. Public comment is sought on whether limiting re-disclosure to four specific circumstances unless such a disclosure was "required by law" is too restrictive, or whether more permissive standards would better facilitate the NPRM goal of fostering the secondary research use of information.

Also, research involving the collection and use of biospecimens or identifiable private information that would qualify for an exemption under section §__.104(e) and (f) must conform to the privacy safeguards proposed in §__.105. A proposed change also appears at §__.115(c),

requiring that IRB records that contain identifiable private information also be safeguarded through compliance with the safeguards proposed at §__.105.

In addition to ensuring that biospecimens and identifiable private information are protected, a benefit of this new provision is that IRBs would not be required to review the individual plans for safeguarding information and biospecimens for each research study, so long as investigators will adhere to them. While there is a presumption that the proposed §__.105 privacy safeguards are sufficient, an IRB may determine that a particular activity requires more than what is discussed in §__.105. Once IRBs are familiar with standard institutional and investigator adopted protections, it is anticipated that they will become more comfortable with the fact that they need not review every protocol for privacy safeguards. In addition, there will be an overall reduction in regulatory burden because IRBs will not have to review security provisions on a case-by-case basis.

Finally, the proposed exemptions found at §__.104(e) and (f), which will permit a larger number of protocols to proceed without IRB review if specific conditions are met, are conditioned on investigators and institutions meeting these privacy and security requirements. Note that there is currently no requirement for an IRB to determine whether investigators are adhering to the §__.105 privacy safeguards for research exempted under §__.104(e) or (f).

5. What would change?

- The NPRM would create a set of standards for the protection of information for research to create an effective and efficient means of implementing appropriate protections for information and biospecimens.
- The NPRM also proposes to include limitations for the use and disclosure of information and biospecimens.
- IRBs would be required to safeguard their records in compliance with the provisions at §__.105 if the records contain identifiable private information.

6. Questions for Public Comment

71. Public comment is sought regarding whether particular information security measures should be required for certain types of information or research activities and, if so, what measures and for what types of information or research. Specifically, should the safeguards be calibrated to the sensitivity of the information to be collected?

72. Are the proposed limitations on re-disclosure more or less restrictive than necessary? Are there additional purposes for which re-disclosure of biospecimens or identifiable private information should be permitted?

D. Harmonization of Agency Guidance (NPRM at §__.101(j))

1. NPRM Goal

From the outset of the development of the Common Rule, the importance of consistency across the Federal Government has been recognized. Each Common Rule department or agency may issue its own guidance regarding the protection of human subjects. Consequently, there may be variations in the guidance issued.

As the label of the Common Rule suggests, there seems to be a compelling case for consistency across Federal departments and agencies regarding guidance on the protections of human subjects. Nevertheless, there are arguments in favor of some departments or agencies imposing specific requirements, apart from the Common Rule, that are tailored to certain types of research. The various agencies that oversee the protection of human subjects range from regulatory agencies, to those agencies and departments that conduct research, and to those that support and sponsor research. In addition, in some cases, statutory differences among the agencies have resulted in different regulatory requirements and agency guidance. Not only do the agencies have different relationships to the research, but they also oversee very different types and phases of research and thus there may be reasonable justifications for differences in guidance. Moreover, achieving consensus across the entire Federal Government may be arduous, preventing timely issuance of guidance.

2. Current Rule

Each Common Rule agency, and the FDA, is authorized to issue its own guidance with regard to interpreting and implementing the regulations protecting human subjects. That guidance may substantially differ from agency to agency.

Currently, there are multiple efforts to address variation in guidance across the Federal Government, but there is no regulatory requirement for agencies to consult other departments prior to issuance of a policy, to the extent appropriate. As a result, inter-departmental communication is at times uneven, leading to potentially avoidable inconsistencies. The Common Rule departments and agencies have procedures for sharing proposed guidance before it is adopted, and these procedures have generally been successful. Additionally, FDA and OHRP have been working closely to ensure harmonization of guidance and regulation to the extent possible, given the differing statutory authorities and regulatory missions.

3. ANPRM Discussion

The ANPRM did not suggest any specific approaches to harmonization but asked for public comment on a set of questions focused on: (1) the extent to which differences in guidance on research protections from different agencies strengthen or weaken protections for human subjects; (2) the extent to which differences in guidance on research protections from different agencies facilitate or inhibit the conduct of research domestically and internationally; and (3) the desirability of all Common Rule agencies issuing one set of guidance.

4. NPRM Proposal

Responses to questions in the 2011 ANPRM about the need for harmonization across Common Rule agencies reflected widespread support for such efforts. Several commenters acknowledged

the difficulty of getting all Common Rule agencies to agree on all issues, as each has a different mission and research portfolio. However, they encouraged seeking harmonized guidance whenever possible.

Thus, the NPRM proposes that the regulations contain language at §__.101(j) requiring consultation among the Common Rule agencies for the purpose of harmonization of guidance, to the extent appropriate, before federal guidance on the Common Rule is issued, unless such consultation is not feasible.

The Department believes this proposal appropriately recognizes the importance of harmonized guidance by creating an expectation that guidance should only be issued after consultation among the Common Rule agencies, while also permitting guidance to be issued without such consultation when it is not feasible. The proposal also recognizes that harmonization will not always be possible or desirable given the varied missions of the agencies that oversee the protection of human subjects and differences in statutory authorities. Although the NPRM proposal is limited to requiring consultation for the purpose of harmonization, the Common Rule agencies may wish to consult with one another before issuing guidance for reasons other than the purpose of harmonization, and the proposal would not preclude this. Some concerns have been expressed that the proposed language in §__.101(j) does not go far enough to mandate harmonization in guidance between Common Rule agencies. Others are concerned that this provision would, in effect, mean that Common Rule agencies issue fewer guidance documents because of lengthy internal government review and approval processes. Public comment is sought about the effectiveness of the consultation language proposed in §__.101(j), and whether

this language should require more (or less) than consultation amongst Common Rule agencies before guidance is issued.

For example, FDA intends to modify its regulations in light of this NPRM, to the extent appropriate, considering its unique statutory framework and regulatory mission. In developing guidance that interprets its human subject protection regulations that mirror the requirements found in the Common Rule, FDA may seek consultation with the Common Rule agencies, to the extent feasible. Further, FDA and OHRP will continue to work together in developing guidance on their respective regulatory requirements that are found both in FDA regulations and in the Common Rule, to the extent feasible.

5. What would change?

- The regulations would contain language at §__.101(j) requiring consultation among the Common Rule agencies for the purpose of harmonization of guidance, to the extent appropriate, before federal guidance on the Common Rule is issued, unless such consultation is not feasible.

6. Question for Public Comment

73. Will the proposed language at §__.101(j) be effective in achieving greater harmonization of agency guidance, and if not, how should it be modified?

E. Cooperative Research (NPRM and Current Rule at §__.114) and Proposal to Cover Unaffiliated IRBs Not Operated by an Institution Holding a Federalwide Assurance (NPRM at §__.101(a))

1. NPRM Goal

The goal is to enhance and streamline the review process, reduce inefficiencies, and hold unaffiliated IRBs directly accountable for regulatory compliance, without compromising ethical principles and protections.

2. Current Rule

Currently, an institution engaged in non-exempt human subjects research conducted or supported by any Federal department or agency that has adopted the Common Rule is required to hold an OHRP-approved FWA or another assurance of compliance approved by the Federal department or agency conducting or supporting the research. The FWA mandates the application of the Common Rule only to certain federally funded research projects. Most institutions voluntarily extend the applicability of the Common Rule to all the research conducted at their institutions, even research not conducted or supported by one of the federal departments or agencies that have adopted the Common Rule.[64] However, such extensions are not required. Many observers have

[64] According to the OHRP's FWA Database, twenty-five percent of institutions with an active FWA have formally extended the Common Rule to all research conducted at those institutions, regardless of funding source (by "checking the box" on their assurance). Comments from the regulated community suggest that most institutions, however, voluntarily follow the requirements of the Common Rule in all research activities conducted at these institutions.

called for legislation that would extend the Common Rule protections to all research with human subjects conducted in the United States, regardless of funding source.

In addition, IRBs not affiliated with an institution holding an FWA are not directly subject to oversight for compliance through the vehicle of the FWA. OHRP's current practice of enforcing compliance with the Common Rule in situations where an institution relies on an external IRB is through the institutions that are engaged in human subjects research, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB. Thus, certain aspects of the regulations are not directly applied to external IRBs.

External IRB review of cooperative research may be problematic given the current lack of direct regulatory accountability and the large volume of cooperative reviews. The inefficiencies of multiple IRB reviews for cooperative studies adds bureaucratic complexity to the review process, and delays initiation of research projects without evidence that multiple reviews provide additional protections to subjects.

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, informed consent forms and other materials, sometimes resulting in hundreds of reviews for one study. When any one of these IRBs requires changes to the research protocol that are adopted for the entire study, investigators must re-

submit the revised protocol to all of the reviewing IRBs. This process can take many months and can significantly delay the initiation of research projects and recruitment of subjects into studies.

In 2006, the FDA issued guidance intended to assist sponsors, institutions, IRBs, and clinical investigators by facilitating the use of a centralized IRB review process in cooperative clinical trials of investigational new drugs.[65]

Currently, the choice to have cooperative research reviewed by a central IRB, or by an IRB at another institution, is voluntary under the Common Rule. In practice, most institutions have been reluctant to replace review by their local IRBs with review by a central IRB.

3. Relevant Prior Proposals and Discussions

The choice to have cooperative research reviewed by a single unaffiliated IRB (or by an external IRB operated by or affiliated with another FWA-holding institution) currently is voluntary. In practice, most institutions have been reluctant to replace review by their local IRBs with review by a single IRB. Participants in two meetings on alternative IRB models co-sponsored by OHRP in November 2005 and November 2006 indicated that one of the key factors influencing institutions' decisions about this issue is OHRP's current practice of enforcing compliance with the Common Rule through the institutions that were engaged in human subjects research,[66] even

[65] See FDA Guidance at: Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials. (2006, March). Retrieved from U.S. Food and Drug Administration: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127013.pdf

[66] In general, an institution is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research

in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB.

In 2009, OHRP issued an ANPRM in the Federal Register requesting information and comments from the public about whether the office should pursue a notice of proposed rulemaking to enable OHRP to hold IRBs and the institutions or organizations operating the IRBs directly accountable for meeting certain regulatory requirements of the Common Rule.[67] OHRP contemplated this regulatory change to encourage institutions to rely on IRBs that are operated by another institution or organization, when appropriate. In this ANPRM, OHRP stated that it believed that such a regulatory change in its enforcement authority might address one of the main disincentives institutions have cited as inhibiting them from exercising the regulatory flexibility that currently permits institutions to implement a variety of cooperative review arrangements and to rely on the review of an IRB operated by another institution or organization. If institutions become more willing to rely on cooperative review arrangements and on review of IRBs operated by other institutions or organizations, this could reduce administrative burdens associated with implementing the Common Rule without diminishing human subject protections.

The ANPRM sought public comment on the feasibility, advantages, and disadvantages of mandating that all domestic (United States) sites in a study involving more than one institution rely on a single IRB for that study. This would apply regardless of whether the study underwent

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through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. Office for Human Research Protections. (2008, October 16). Guidance on Engagement of Institutions in Human Subjects Research. Retrieved from Policy & Guidance: http://www.hhs.gov/ohrp/policy/engage08.htmll

[67] 74 FR 9568 (Mar.5, 2009).

convened review or expedited review. Further, it would only affect which IRB would be designated as the reviewing IRB for institutional compliance with the IRB review requirements of the Common Rule. It would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal ethics reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule.

Based on public comments received to the 2009 ANPRM[68] on the issue of IRB accountability and to address institutions' concerns about OHRP's practice of enforcing compliance with the Common Rule through the institutions that are engaged in human subjects research, the 2011 ANRPM also suggested that appropriate accompanying changes could be made in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory requirements.[69] This change was discussed only for United States sites in multi-institutional studies. The ANPRM suggested that, in most cases, independent local IRB reviews of international sites are appropriate because it might be difficult for an IRB in the U.S. to adequately evaluate local conditions in a foreign country that could play an important role in the ethical evaluation of the study.

In late 2014, NIH issued a Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multisite Research. The response to NIH's proposed policy was robust and largely supportive, with many institutions citing both reduced duplication of effort and faster initiation of research as important factors. A minority, however, pointed to the

[68] 74 FR 9578 (Mar. 5, 2009).
[69] 74 FR 9578 (Mar. 5, 2009). Also available at http://www.hhs.gov/ohrp/newsroom/rfc/com030509.html.

importance of maintaining independent local IRB review, and expressed doubt over the anticipated efficiencies and cost savings that would be incurred through a centralized model. SACHRP commented on this draft policy, and was generally supportive of voluntary increased use of a single IRB for multi-site studies, as such use may decrease differences among site implementation of protocols. SACHRP concluded that a uniform mandate of single IRB review for all domestic multi-site studies was premature, and recommended a more incentivized approach at this time.[70]

4. NPRM Proposals

These issues attracted a large number of comments to the 2011 ANPRM, and revealed nearly evenly divided perspectives. Investigators and disease advocacy groups tended to favor the single IRB review requirement. IRB and institutional representatives tended to be opposed to the possible requirement, though many indicated single IRB review should be encouraged. Support was especially strong for single IRB review for cooperative clinical trials for which the evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent form and process generally do not require the unique perspective of a local IRB. Moreover, depending on the nature of the study, FDA may not permit differences in protocols across sites, which further bolstered commenters' views that the requirements be harmonized across the Common Rule and FDA requirements. Commenters reported incidences of IRBs continuously second-guessing each other, which delayed studies to the point that subject

[70] Secretary's Advisory Committee on Human Research Protections. (2015). Recommendations Regarding the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-site Research. Retrieved from Office for Human Research Protections : http://www.hhs.gov/ohrp/sachrp/commsec/useofasingle_irb.html

recruitment opportunities were foregone or lost. This problem seemed especially critical in studies of rare diseases and cancers, which nearly always involve multiple research sites.

Support for the use of a single IRB, however, was not restricted to clinical trials. Several commenters cited long delays and burdensome requirements resulting from multiple reviews of studies in the behavioral and social sciences. In addition to the view that these administrative requirements do not enhance protections, supporters of a single IRB review of cooperative studies cited the frequent need for maintaining consistency across sites, which can be degraded by multiple reviews.

Despite support for the ANPRM suggestion, several commenters expressed concern about making such a provision mandatory, stating that the current regulations at §__.114 permit the use of joint review arrangements for cooperative research. They noted that although this option exists, institutions might be hesitant to use it because of liability concerns and the unwillingness of institutions or IRBs to rely on the judgment of other institutions or IRBs. However, several commenters expressed concern about signaling the acceptability of a single IRB for review while allowing institutions to continue to conduct their own ethics review, fearing that such a policy would not correct the current situation, which tends to favor multiple reviews. Thus, they commented that mandating a single IRB might be the only way to achieve the goals of streamlining review while ensuring protections.

Another issue raised was the need to set clearer expectations of the responsibilities of local IRBs that are not designated as the central IRB. A number of commenters supporting the requirement

for a central IRB also requested that OHRP issue guidance on how to select the IRB, responsibilities of all parties, and compliance and enforcement policies. Several commenters also requested that OHRP develop a template for reliance agreements to replace inter-institutional agreements currently in use.

Those who expressed concern about the use of a single IRB said some studies, especially in the behavioral and social sciences, might involve significant contextual issues reflecting community norms, standards, and practices, or local culture and customs. Use of a distant IRB might not consider and best protect subjects based on community norms. Others noted that such concerns can be addressed by investigators or IRBs submitting "points to consider" regarding significant contextual or cultural considerations of relevance to their site.

A primary issue posed by those opposed to mandating use of a single IRB in cooperative studies focused on potential loss of accountability and increased liability for the institutions where the research is conducted but where the reviewing IRB is not located.

Taking into consideration this public debate and various sources of public comments, the NPRM proposes a requirement at §__.114(b)(1) mandating that all institutions located in the United States engaged in cooperative research rely on a single IRB as their reviewing IRB for that study. Under proposed §__.114(b)(2), this requirement would not apply to: (1) cooperative research for which more than single IRB review is required by law (e.g., FDA-regulated devices); or (2) research for which the Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular study.

Based on comments to OHRP's 2011 ANPRM, the NPRM also proposes to add a new provision at §__.101(a) that would explicitly give Common Rule departments and agencies the authority to enforce compliance directly against unaffiliated IRBs that are not operated by an assured institution. This change is proposed to address concerns about OHRP's current practice of enforcing compliance with the Common Rule through the institutions that are engaged in human subjects research, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB. In large part, this change was made to facilitate the use of a single IRB in cooperative research, allowing OHRP to enforce compliance with the Common Rule through non-compliant external IRBs rather than the institutions that were engaged in human subjects research. This proposal should encourage institutions to be more willing to rely on a single IRB for cooperative research as required under the NPRM proposal at §__.114. It would reassure institutions using an external IRB because compliance actions could be taken directly against the IRB responsible for the flawed review, rather than the institutions that relied on that review.

Some public commenters responding to the 2011 ANPRM cautioned that extending compliance oversight to external IRBs might serve as a disincentive for some IRBs to be the IRB of record for cooperative research. A majority of commenters expressed an opposing view; that is, holding external IRBs directly accountable for compliance with the regulations would increase the comfort level of institutions in accepting the regulatory review of an external IRB.

Related to this issue is a new provision proposed at §__.103(e) regarding policies for documenting an institution's reliance on an external IRB. That provision states that for non-exempt research involving human subjects covered by this policy that takes place at an institution in which IRB oversight is conducted by an IRB that is not affiliated with the institution, the institution and the IRB should establish and follow written procedures identifying the compliance responsibilities of each entity. These procedures should be set forth in an agreement between the institution and the IRB specifying the responsibilities of each entity in ensuring compliance with the requirements of this policy.

This would only apply to U.S.-conducted portions of studies because the flexibility to make use of external local IRB reviews of international sites should be maintained; it might be difficult for an IRB in the United States to adequately evaluate local conditions in a foreign country that could play an important role in the ethical evaluation of the study.

This policy would apply regardless of whether the study underwent convened review or expedited review. This proposal only affects the decision regarding how an IRB would be designated as the reviewing IRB for institutional compliance with the IRB review requirements of the Common Rule. The reviewing IRB is expected to be selected either by the funding agency or, if there is no funding agency, by the lead institution conducting the study. An agency may solicit input regarding which IRB would be most appropriate to designate as the IRB of record. Public comment is sought on how this will work in practice.

This policy would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal IRB reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule. Although a local IRB may conduct its own additional internal review, such a review would not be binding on the local site if not adopted by the single IRB, and the terms of it would not be enforced by OHRP.

Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most studies can be addressed through mechanisms other than local IRB review. For research where local perspectives might be distinctly important (e.g., in relation to certain kinds of vulnerable populations targeted for recruitment), local IRB review could be limited to such consideration(s); but again, IRB review is not the only mechanism for addressing such issues. The evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent form and process generally do not require the unique perspective of a local IRB.

The proposal also modifies the current regulations by removing the requirement that only with the approval of the department or agency head may an institution participating in a cooperative project enter into a joint review arrangement, rely upon the review of another IRB, or make similar arrangements for avoiding duplication of effort. Such approval is no longer required.

Some detractors of mandated single IRB review for cooperative research point to concerns regarding implementation logistics, and the time necessary to establish new policies, procedures,

and agreements; recognizing this concern, the proposed compliance date is three years from the publication of the final rule.

5. What would change?

- IRBs not affiliated with an assured institution that review research covered by the Common Rule would be subject to direct compliance oversight regarding IRB regulatory requirements.
- All U.S. institutions engaged in a cooperative study would rely upon a single IRB for that study, with some exceptions.

6. Questions for Public Comment

74. Is mandated single IRB review for all cooperative research a realistic option at this time? Please provide information about the likely costs and benefits to institutions. Will additional resources be necessary to meet this requirement in the short term? Should savings be anticipated in the long run?

75. What areas of guidance would be needed for institutions to comply with this requirement? Is there something that OHRP could do to address concerns about institutional liability, such as the development of model written agreements?

76. Would it be useful for this requirement to include criteria that Federal departments or agencies would need to apply in determining whether to make exceptions to the use of a single IRB requirement? If so, what should these criteria be?

77. Are the exceptions proposed appropriate and sufficient, or should there be additional exceptions to this mandate for single IRB review than those proposed in the NPRM? If additional exceptions should be included, please provide a justification for each additional exception recommended.

78. Is three years appropriate timing to establish compliance with this provision?

F. Changes to Promote Effectiveness and Efficiency in IRB Operations

1. Continuing Review of Research (NPRM at §__.109(f); current Rule at §__.109(e))

a. NPRM Goal

The goal is to reduce or eliminate the need for continuing review in specific circumstances, thereby reducing regulatory burden that does not meaningfully enhance protection of subjects.

b. Current Rule

The current regulations at §__.109(e) require that IRBs conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year. Except when an expedited review procedure is used, continuing review of research must occur at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas. In order for research undergoing continuing review to be approved, it must receive the approval of a majority of those members present at the meeting (§__.108(b)).

An IRB may use an expedited review procedure to conduct continuing review of research for some or all of the research appearing on the list of research eligible for expedited review[71] and found by the reviewer(s) to involve no more than minimal risk. OHRP may restrict, suspend, terminate, or choose not to authorize an IRB's use of the expedited review procedure (§__.110(d)).

c. ANPRM Discussion

The ANPRM requested comments on eliminating continuing review for all minimal risk studies that undergo expedited review, unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects. For studies initially reviewed by a convened IRB, continuing review would not be required, unless specifically mandated by the IRB, after the study reaches the stage where procedures are limited to either (1) analyzing data (even if it is

[71] See Office for Human Research Protections (OHRP) – Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure. November 9, 1998, http://www.hhs.gov/ohrp/policy/expedited98.html.

identifiable), or (2) accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition or disease.

d. NPRM Proposals

The NPRM proposes at §__.109(f) eliminating continuing review for many minimal risk studies (namely those that qualify for expedited review), unless the reviewer documents why continuing review should take place (as would be required by §__.115(a)(8)). Moreover, for studies initially reviewed by a convened IRB, continuing review would not be required, unless specifically mandated by the IRB, after the study reaches the stage where it involves one or both of the following: (1) analyzing data (even if it is identifiable private information), or (2) accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition or disease.

In addition, continuing review would not be required for research involving certain secondary research using information and biospecimens that requires limited IRB review in order to qualify for exemption under §__.104(f)(1).

Further, the NPRM proposes at §__.109(f)(2) that an IRB must receive annual confirmation that such research is ongoing and that no changes have been made that would require the IRB to conduct continuing review (that is, the study still qualifies for expedited review because it still meets the criteria listed above and still involves no greater than minimal risk). This confirmation allows the IRB to administratively account for research that is occurring without continuing

review. Investigators would continue to be required to submit changes to the protocol to the IRB. This requirement aims to address concerns some might have about institutional liability relating to the status of ongoing research, the possibility for increased noncompliance among investigators no longer required to "check in," and possible breakdowns in lines of communications between investigators and IRBs. Institutions will have significant flexibility in how they implement this requirement. For example, some might rely on an automated electronic communication with the investigator at one-year intervals after the study was initiated that might merely require the investigator to type "yes" indicating that the study is ongoing and that no changes have been made. It is therefore anticipated that this requirement can be met with minimal time and effort on the part of investigators and IRBs. Investigators would still have the current obligations to report various developments (such as unanticipated problems or proposed changes to the study) to the IRB.

If an IRB chooses to conduct continuing review even when these conditions are met, the rationale for doing so must be documented according to a new provision at §__.115(a)(8).

The NPRM, at §__.115(a)(3), proposes a new requirement for IRBs to maintain records of continuing reviews. Because the NPRM proposes a new provision that eliminates the need for continuing review under specific circumstances (§__.109(f)(1)), the NPRM at §__.115(a)(8) also proposes that IRBs need to justify the need for continuing review in cases where they will not follow the provision in §__.109(f)(1).

e. What would change?

- Continuing review would be eliminated for all studies that undergo expedited review, unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects. For studies initially reviewed by a convened IRB, once certain specified procedures are all that remain for the study, continuing review would not be required, unless specifically mandated by the IRB. However, investigators would be required to provide annual confirmation to the IRB that such research is ongoing and that no changes have been made that would require the IRB to conduct continuing review.
- Continuing review would not be required for research involving certain secondary research using information and biospecimens that requires limited IRB review in order to qualify for exemption under §__.104(f)(1).

2. Expedited Review Procedures and the Definition of "Minimal Risk" (NPRM at §§__.110 and __.102(j))

a. NPRM Goal

IRBs report challenges in assessing the level of risk presented by some studies in order to make the critical minimal risk determination. This is, in part, due to the difficulties in applying the current definition of minimal risk within the Common Rule, particularly because the terms "ordinarily encountered in daily life" and "routine physical or psychological examinations" are not clarified. The goal is to help eliminate this ambiguity as it pertains to expedited review, and improve the efficiency and consistency of minimal risk determinations for some activities.

b. Current Rule

The concept of "minimal risk" is central to numerous aspects of the Common Rule, the determination of which affects the type of review required, considerations for IRBs in the review process, and the frequency of review. In sum, the review process has been calibrated, for the most part, to the risk of the research.

The current definition of minimal risk at §___.102(i) encompasses research activities where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Under the Common Rule at §__.110, a research study can receive expedited review if the research activities to be conducted appear on the list of activities published by the Secretary of HHS that are eligible for such review,[72] and is found by the reviewer(s) to involve no more than minimal risk. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB. Research that is eligible for expedited review requires continuing review at least annually.

[72] *See* Office for Human Research Protections (OHRP) – Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure. November 9. 1998, http://www.hhs.gov/ohrp/policy/expedited98.html.

c. ANPRM Discussion

The ANPRM suggested updating the current list of research activities eligible for expedited review; this list was last updated in 1998. It also considered mandating that a federal panel periodically (such as every year or every two years) review and update the list, based on a systematic, empirical assessment of the levels of risk. This would provide greater clarity about what would be considered to constitute minimal risk, and create a process that allows for routinely reassessing and updating the list of research activities that would qualify as minimal risk. The ANPRM asked for public comments on categories of research that should be considered for addition to the current list.

The ANPRM asked for public comment on whether the current regulatory definition of minimal risk is appropriate. The ANPRM further suggested that the "default" assumption would be that a study otherwise eligible for expedited review will be considered minimal risk unless a reviewer documents the rationale for classifying the study as involving more than minimal risk.

Finally, the ANPRM discussed the idea that continuing review would not be required of studies that are eligible for expedited review unless the reviewer, at the time of initial review, determines that continuing review is required, and documents why. In follow-up to this discussion, the ANPRM asked for comments on whether IRBs should be required to report instances when they overrode the default presumption that research appearing on the posted list did not warrant review by a convened IRB.

d. NPRM Proposal

Based on public comments on the ANPRM, the NPRM proposes changes to the current regulatory language at §__.110(b)(1) regarding expedited review, and will allow expedited review to occur for studies on the Secretary's list unless the reviewer(s) determine(s) that the study involves more than minimal risk. This is in contrast to the current regulations, which require that an IRB use the expedited review procedure only if the reviewer determines that the research involves no more than minimal risk; in addition, OHRP has indicated that the activities on the current list should not be deemed to be of minimal risk simply because they are included on the list. Therefore, this proposed change represents a change to the default position, and now says that research included on the list only involves minimal risk, unless the IRB makes a determination that the research is actually greater than minimal risk. Thus, it is anticipated that more studies that involve no more than minimal risk would undergo expedited review, rather than full review, which would relieve burden on IRBs.

This proposal is in line with public comment to the 2011 ANPRM. Commenters overwhelmingly welcomed the clarification that categories of research found on the published list should be presumed to be minimal risk. However, commenters were largely opposed to requiring IRBs to report instances when they conducted a review by the convened membership (versus an expedited review) for studies appearing on the list. They were opposed because of the additional administrative burden and also because they felt such a requirement would undermine the purview of local review and open IRBs up to second-guessing by OHRP.

Public comments to the 2011 ANPRM expressed both a desire to retain the current definition (slightly less than half) and a desire for changing it (slightly more than half). There were few common themes in the suggested changes to the language other than seeking clarification on what baselines an IRB should consider in determining the meaning of "daily life" and "routine physical or psychological examinations." Several commenters acknowledged the difficulty of arriving at a concise definition for all circumstances. Those opposed to changing the definition said that IRBs generally understand how to interpret the language and that difficult or challenging application of the definition will persist regardless of the definition for those areas of research where risks are difficult to assess. Commenters recognized that the risks encountered in daily life can vary greatly depending on many factors, for example, where people live, what kind of work they are involved in, what their social and economic environment is, and their baseline health status. Thus, IRBs need to consider all of these issues in making a determination about the level of risk.

Thus, the NPRM does not propose to modify the definition of minimal risk (NPRM at §__.102(j)), but rather proposes adding to the definition a requirement that the Secretary of HHS create and publish a list of activities that qualify as "minimal risk." This Secretary's list will be re-evaluated periodically, but at least every 8 years, based on recommendations from federal departments and agencies and the public. Note that this will not be an exhaustive list of all activities that should be considered minimal risk under the Common Rule, but will allow IRBs to rely on the determination of minimal risk for activities appearing on the list. IRBs will still need to make minimal risk determinations about activities that do not appear on this list.

In addition, the NPRM proposes to eliminate the parenthetical phrase "of one year or less" at §__.110(b)(2) since annual continuing review of research eligible for expedited review and research that progresses to the point of only involving specified limited activities will no longer be required for all ongoing human subjects research. The NPRM also proposes that the regulations be revised at §__.110(a) to require evaluation of the list of expedited review categories every 8 years, followed by publication in the Federal Register and solicitation of public comment. A revised list will be prepared for public comment outside the scope of the NPRM.

For several reasons, the NPRM proposes no changes in the requirement that expedited review be conducted by an IRB member. First, public comments on the 2011 ANPRM were divided on the value of allowing a non-IRB member to conduct such reviews. Those with concerns questioned whether permitting someone other than an IRB member to conduct expedited review would have unintended consequences, such as either increasing or decreasing the number of studies deemed acceptable for expedited review, or by increasing liabilities for the institution. Second, IRB staff members would likely constitute the pool of non-IRB members qualified to conduct expedited review, and the current regulations permit IRB staff members to be IRB members. HHS does not believe a regulatory change is warranted to facilitate expedited review.

Finally, the NPRM contains a requirement at §__.115(a)(9) that IRBs document the rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk (i.e., an override of the presumption that studies on the Secretary's list are minimal risk). Such documentation could provide a basis for the Secretary's future

determinations about the appropriateness of the list, and allow for greater internal consistency at institutions. In response to public comment on the 2011 ANPRM, the NPRM does not propose to require that institutions report such determinations directly to OHRP. Commenters were largely opposed to requiring IRBs to report instances when they conducted a review by the convened membership (versus an expedited review) for studies appearing on the list. They were opposed because of the additional administrative burden and also because they felt such a requirement would undermine the purview of local review and open IRBs up to second-guessing by OHRP.

e. What would change?

- Expedited review can occur for studies on the Secretary's list unless the reviewer(s) determine(s) that the study involves more than minimal risk.
- Evaluation of the list of expedited review categories would occur every 8 years, followed by publication in the Federal Register and solicitation of public comment.
- IRBs will be required to document their rationale when they override the presumption that studies on the Secretary's expedited review list involve greater than minimal risk.
- The Secretary of HHS will create and publish and maintain a list of activities that should be considered minimal risk.

f. Questions for Public Comment

79. How often should the Secretary's list of minimal risk activities be updated? Should advice be solicited from outside parties when updating the list?

80. Is this Secretarial list of minimal research activities a useful tool for the research community, or does it represent a loss of IRB flexibility in risk determination?

G. Proposed Changes to IRB Operational Requirements

1. Proposed Criteria for IRB Approval of Research (NPRM at §___.111)

a. NPRM Goals

These revisions modernize the rule by (1) creating new forms of IRB review for activities relating to storing or maintaining data and biospecimens for later secondary use, and for the review of studies involving certain types of such secondary use; (2) revising two of the existing criteria for approval of research, where there are special considerations related to the involvement of vulnerable populations and for privacy and confidentiality of data provisions; and (3) adding a provision regarding plans to review the return of individual results to participants.

b. Current Rule

There are several determinations that an IRB must generally make before it can approve a study, which are spelled out in current Common Rule at §__.111. These relate, among other things, to minimizing risks to subjects, determining that there is an appropriate relationship between risks

and benefits, and assuring the equitable selection of subjects. The regulations generally require all of these determinations to be made with regard to any study that must undergo IRB review.

c. ANPRM Discussion

The ANPRM asked whether all of the §__.111 criteria should still be required for approval of studies that qualify for expedited review, and if not, which ones should not be required. Currently, before an IRB may approve a research study, including research that is being reviewed under an expedited procedure, the IRB must find that the criteria at §__.111 have been met.

d. NPRM Proposals

Based on comment to the 2011 ANPRM, the NPRM does not propose to modify the §__.111 criteria that apply to research reviewed under the expedited procedure versus research reviewed under full board review. The NPRM does however propose a number of changes regarding the criteria for IRB approval of research, including (1) creating a new form of IRB review for activities relating to storing or maintaining data and biospecimens for later secondary use; (2) revising two of the existing criteria for approval of research, where there are special considerations related to the involvement of vulnerable populations and for privacy and confidentiality of data provisions; and (3) adding a provision regarding plans to review the return of individual results to participants.

The first set of changes relates to updating the IRB review criteria for research activities relating to storing or maintaining information and biospecimens, and to the secondary use of such information and biospecimens. Paragraph (a)(9)(i) of proposed §__.111 would apply to storage or maintenance for secondary research use of biospecimens or identifiable private information. This provision would eliminate the need for an IRB to make the usual determinations with regard to such an activity. Instead, the IRB would be required to determine that the procedures for obtaining broad consent to the storage or maintenance of the biospecimens or information were appropriate, and met the standards included in the introductory paragraph of §__.116. In addition, if these storage and maintenance activities involved a change for research purposes from the way the biospecimens or information had been stored or maintained, then the IRB would have to determine that the biospecimen and privacy safeguards at §__.105 are satisfied for the creation of any related storage database or repository. Note that in many instances there will be no such change. For example, an individual could sign a consent form allowing broad unspecified future research use of information contained in their medical records, and that information would remain where it is, but be tagged in some manner to indicate that the individual has provided such consent.

This in effect means that the default for such secondary research studies using either biospecimens or identifiable information will be that the initial broad consent would be sufficient, and that there will be no need to obtain a new consent from individuals for each specific research study that is conducted with the biospecimens and information.

The second proposal, relating to vulnerable subjects, is intended to address an inconsistency in the current regulations among three provisions in the current Common Rule that address requirements related to the consideration of vulnerable populations: §§__.107(a), __.111(a)(3), and __.111(b). Under the current Rule, only §__.111(b) of these three provisions provides that vulnerability to coercion or undue influence is the type of vulnerability that should be considered. It is proposed that the criterion at §__.111(a)(3) be revised to align with the language of §__.111(b) to reflect that the vulnerability of the populations in these research studies should be considered to be a function of the possibility of coercion or undue influence, and that this vulnerability alone should be the IRB focus of concern with respect to this criterion. The proposed change is intended to provide greater consistency and clarity in IRB consideration of vulnerability of subject populations in research activities and appropriate protections. A comparable change is also proposed at §__.107(a), pertaining to IRB membership. In addition, of these same three provisions in the current Rule, only §__.107(a) identifies "handicapped" individuals (which the NPRM proposes be changed to "physically disabled" individuals as discussed below in section II.G.2.c. of the preamble) as a vulnerable category of subjects. Therefore, to enhance consistency and clarity among these three provisions, it is proposed that the term "physically disabled" be inserted at §__.111(a)(3) and (b). This would mean that physically disabled persons would be among the individuals that the IRB may consider in determining that the selection of subjects is equitable (§__.111(a)(3)), and that the IRB may consider to be vulnerable to coercion or undue influence (§__.111(b)). Public comment is being sought on these proposed changes to the provisions related to vulnerable populations. Since it is proposed that the only vulnerability that needs to be considered is vulnerability to coercion or undue influence, and not other types of vulnerability, it is appropriate to review the subject

populations to determine whether all of these subject populations identified in these three provisions should be considered vulnerable to coercion or undue influence. In particular, public comment is sought about whether pregnant women and those with physical disabilities should be characterized as vulnerable to coercion or undue influence. Whether or not these subpopulations are considered vulnerable to coercion or undue influence would not affect the applicability of subpart B.

The third proposed change would be an addition of paragraph (a)(8) to §__.111 clarifying that if an investigator submits as part of the protocol a plan for returning individual research results, the IRB will evaluate the appropriateness of the plan. IRBs need not determine whether there should be a plan for returning individual research results. Although many IRBs probably already review plans for return of results, many studies do not include this feature. Challenges can arise regarding return of individual research results when it is not clear if the findings have clinical validity or utility, or when the knowledge imparted may cause psychological distress or social harm. These issues have been the subject of frequent discussion, particularly regarding the Clinical Laboratory Improvement Amendments of 1988, 42 U.S.C. 263a.[73,74,75]

An additional change is related to the proposed changes at §__.105, and would clarify that it is not an IRB responsibility to review the security plans for biospecimens and identifiable private information for every protocol (i.e., on a case-by-case basis). It is assumed that once institutions

[73] Presidential Commission for the Study of Bioethical Issues. (2013, December). Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts. Retrieved from Presidential Commission for the Study of Bioethical Issues: http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf

[74] Wolf SM et al. Managing incidental findings in human subjects research: Analysis and recommendations. J Law Med Ethics 2008 Summer; 36(2):219-248, 211.

[75] Ofri D. 2013. Medicine's problem of 'incidental findings.' *Atlantic Monthly*.

and investigators have established policies and procedures for compliance with the new privacy safeguards at §__.105 (and it is expected that many already have already such procedures in place), that IRBs will be confident in omitting that aspect of their review of research, as it does not pose unusual privacy or security risks to subjects. It is proposed that this requirement will be modified to recognize that the requirements at §__.105 will apply to all non-excluded research (unless the criteria for exemptions are met). The default position should be that if the privacy safeguards at §__.105 are being met, there is no need for additional IRB review of a research study's privacy and security protections. However, there might be extraordinary cases in which an IRB determines that privacy safeguards above and beyond those called for in §__.105 are necessary. Therefore, it is proposed that IRBs will be responsible for ensuring there are adequate provisions to protect the privacy of subjects and to maintain the security of data only if the IRB determines that the protections required in §__.105 are insufficient.

e. What would change?

- A new version of more limited IRB approval criteria would be created for activities relating to the storage or maintenance of biospecimens and identifiable private information for the purposes of later doing secondary research with them.
- IRBs considering the §___.111(a)(3) approval criterion regarding equitable selection of subjects would need to focus on issues related to coercion or undue influence in research with vulnerable populations and not other considerations related to vulnerability.

- Physically disabled persons would be among the individuals that the IRB may consider in determining that the selection of subjects is equitable (§__.111(a)(3)), and that the IRB may consider to be vulnerable to coercion or undue influence (§__.111(b)).
- IRBs would need to consider the requirements for investigators to protect information, and biospecimens as a criterion for approval of research only if they find the protections under §___.105 are not sufficiently protective.
- If a plan for returning research results is included as part of a protocol, IRBs would be required to determine whether the plan is appropriate. IRBs would not be required to determine whether such a plan is needed.

f. Questions for Public Comment

81. What should IRBs consider when reviewing the plans for returning research results, for example, what ethical, scientific, or clinical concerns?

82. Is the §___.111(a)(3) and (b) focus on issues related to coercion or undue influence in research with vulnerable populations, and not other considerations related to vulnerability, appropriate? Note that this focus also appears in proposed §___.107(a).

83. Should pregnant women and those with physical disabilities be included in the category of subpopulations that may be vulnerable to coercion or undue influence?

2. Proposed Revisions to IRB Operations, Functions, and Membership Requirements

a. NPRM Goal

The goal is to improve IRB operations and make relevant sections consistent with other areas of the NPRM.

b. Current Rule

The current Rule outlines IRB functions and operations at §§__.108 and __.103, and membership requirements at §__.107.

c. NPRM Proposals

The NPRM contains several proposals for changes in IRB operations, functions, and membership requirements. First, the requirements for recordkeeping by IRBs no longer appear in §__.103 of the rule. They are now described in §__.108(a)(2), (3), and (4).

Also as previously discussed, IRBs would be required to safeguard their records in compliance with the privacy protections described in proposed §__.105 if the records contain individually identifiable information.

Finally, there are four changes to the IRB membership requirements at §__.107(a). The first change is the elimination of the requirement that IRBs not consist entirely of individuals of one

gender or profession. This provision is unnecessary, because the requirement that IRB membership reflect members of varying backgrounds and diversity, including gender, will accomplish the same effect. The deletion of this provision in the NPRM is not intended to alter the composition of IRBs from what had been established in the current Rule.

For the reasons discussed above in section II.G.1.d, three additional changes are proposed to §__.107(a). It is proposed that §__.107(a) be modified so that consideration of vulnerability of a subject population would be limited to vulnerability to coercion or undue influence. This proposed change is consistent with the proposal at §___.111(a)(3). The proposed change is intended to result in greater consistency and clarity in IRB consideration of vulnerability of subject populations in research activities and appropriate protections.

The third change in §__.107(a) is the insertion of "economically or educationally disadvantaged persons" as an example of a vulnerable population, requiring an IRB to give consideration to membership expertise in this area. This language is already included in the current Rule at §___.111(a)(3) and §___.111(b). Adding this category of individuals to those who may be considered vulnerable to coercion or undue influence at §__.107(a) is intended to create greater consistency among these three provisions.

In order to modernize the regulatory language, the fourth change in proposed §__.107(a) is the replacement of the term "handicapped" persons with "physically disabled persons" as an example of a vulnerable population, requiring an IRB to give consideration to membership expertise in this area.

d. What would change?

- The provision regarding IRBs avoiding membership that consists entirely of individuals of one gender or profession would be eliminated because the requirement that IRB membership reflect members of varying backgrounds and diversity, including gender, would accomplish the same goal.
- The provision regarding the IRB's expertise in the review of research involving a vulnerable category of subjects would be limited to the subjects' vulnerability to coercion or undue influence
- The phrase economically or educationally disadvantaged persons is included as an example of a vulnerable category of subjects, requiring an IRB to give consideration to membership expertise in this area.
- The term "handicapped" persons is replaced with "physically disabled persons" as an example of a vulnerable category of subjects, requiring an IRB to give consideration to membership expertise in this area.

e. Question for Public Comment

84. Should populations be considered vulnerable for reasons other than vulnerability to coercion or undue influence? Are the proposed categories appropriate?

H. Other Proposed Changes

1. Proposal to Extend the Common Rule to All Clinical Trials (with Exceptions) (NPRM at §__.101(a)(1))

a. NPRM Goals

The goal of this proposal is to ensure that studies that generally pose the most risk to potential subjects (such as surgical clinical trials), are encapsulated by the Common Rule. The proposal attempts to balance the goals of ensuring that studies where the Common Rule provides meaningful protections to subjects are covered under the rule, while studies where the administrative burdens of the Common Rule outweigh any potential benefits to subjects are not covered.

b. Current Rule

The Common Rule applies to all research involving human subjects that is conducted or supported by a Federal department or agency that has adopted the policy (§__.101(a)).

c. ANPRM Discussion

The ANPRM discussed the possibility of the Common Rule applying to all studies, regardless of funding source, that are conducted by a U.S. institution that receives some federal funding for human subjects research from a Common Rule agency.

The ANPRM also asked the public to consider a regulatory option to partially fulfill the goal of extending Common Rule protections to all human subjects research in the United States. The discussed policy would require domestic institutions that receive some federal funding from a Common Rule agency for non-exempt research with human subjects to extend the Common Rule protections to all human subjects research studies conducted at their institution.

d. NPRM Proposal

In response to ANPRM feedback, the Common Rule NPRM proposes an extension that would ensure that clinical trials are covered by the Common Rule if conducted at an institution in the United States that receives federal support for non-exempt and non-excluded human subjects research, regardless of the funding source of the specific clinical trial.

Note that the purpose of the clinical trials extension is to ensure that clinical trials that would otherwise not be covered by some body of federal research ethics regulations are covered. To that end, if a clinical trial is already subject to FDA oversight but not Common Rule oversight, since that clinical trial is subject to human subjects protection regulations, this change would not affect it. Also note that this proposed extension is based on whether an institution receives funding specifically for non-exempt and non-excluded research. This is because the Common Rule departments and agencies have a more substantial relationship with institutions that receive support from a Common Rule department or agency to conduct non-exempt and non-excluded

human subjects research than those institutions that receive such support for only exempt and excluded human subjects research.

Although supporting the principle that all human subjects research regardless of funding source should be conducted ethically, public commenters generally expressed concern and caution about the ANPRM consideration for a variety of reasons. Behavioral and social science investigators thought that this approach would unnecessarily bring less-than-minimal-risk research funded by non-federal sources (e.g., surveys or observational studies supported by the nonprofit sector) under burdensome regulatory requirements while not enhancing protections. Some commenters argued that the increased regulatory burden that would ensue was not warranted and would shift scarce oversight resources to review of research studies that are generally non-problematic and frequently supported by non-federal funds, such as some student or institutional research.

Others argued that such a change was an overreach of federal oversight and constituted an unfunded mandate. Commenters from large academic research institutions felt that this change inappropriately focused heavily on academic institutions, which generally extend protections to all human subjects research at their institution, even if they have not "checked the box"[76] on their FWA indicating that they do so. They argued that such a change would not reach those

[76] The FWA covers all non-exempt human subjects research at the submitting institution that is conducted or supported by HHS, or funded by any other federal department or agency that has adopted the Common Rule and relies upon the FWA. It is not project specific. Domestic institutions may voluntarily extend their FWA (and thus a Common Rule department or agency's regulatory authority) to cover all human subjects research at the submitting institution regardless of the source of support for the particular research activity. See Office for Human Research Protections. (2011, June 17). What research does the Federalwide Assurance (FWA) cover? Retrieved from Frequently Asked Questions: http://www.hhs.gov/ohrp/policy/faq/assurance-process/what-research-does-fwa-cover.html

institutions already operating outside the federal research system and would limit flexibility in making risk-based determinations about the levels of review required.

Industry also expressed concern about having to comply with two sets of regulations, that is, FDA regulations as well as the Common Rule. The ANPRM did not clarify that the changes under consideration would not require compliance with the Common Rule of non-federally funded research subject to regulation by FDA. However, there might continue to be research that would be subject to both sets of regulations involving federal funding of research concerning an FDA-regulated product.

Those commenters who supported a formal extension of the regulations cited the need to have one set of standards for all research, regardless of funding source; however, many noted that absent legislation covering all human subjects research conducted in the United States, it would be difficult to cover all research through a regulatory approach alone—gaps would still remain.

Thus, the NPRM proposes changes in the regulatory language at §__.101(a)(2) to state that the policy extends to all clinical trials as defined by this policy, irrespective of funding source, that meet all of three conditions: (1) The clinical trials are conducted at an institution that receives support from a federal department or agency for human subjects research that is not excluded from this policy under §__.101(b)(2), and the research does not qualify for exemption in accordance with §__.104; (2) The clinical trials are not subject to FDA regulation; and (3) The clinical trials are conducted at an institution located within the United States.

For purposes of this policy, the NPRM proposes at §__.102(b) that a clinical trial be a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. By the term "behavioral outcomes," the NPRM contemplates the reality that clinical trials may occur outside of the biomedical context. The studies addressed in the proposed definition of clinical trial at §__.102(b) are more likely to involve greater-than-minimal risk, and, therefore, require the highest level of oversight. Limiting the extension of the regulations to only the highest risk research is consistent with the goal of a more risk-based approach to review. For example, surgical clinical trials that do not receive support from a Common Rule department or agency often are outside of the scope of FDA's human subjects protection regulations. Thus, many of these unfunded activities are currently not subject to the protections afforded by the human subjects protection system. This NPRM proposal would cause many of these trials to come under the purview of the Common Rule.

e. What Would Change?

- Clinical trials as defined by proposed §__.102(b), irrespective of funding source, would be subject to oversight, given specified conditions.

f. Questions for Public Comment

85. Public comment is sought on whether there might be unintended consequences from the clinical trials expansion proposed in the NPRM in §__.101(a)(2)(i)). Unintended consequences may include an increase in burden or costs, or an inappropriate redistribution of costs.

86. Public comment is sought as to whether the criterion that the policy extends to all clinical trials conducted at an institution that receives federal support (see the NPRM at §__.101(a)(2)(i)) should be further clarified in some way. For example, should it specify a timeframe for support (e.g., within the past number of years), or a minimum monetary threshold value?

87. Public comment is sought on whether the definition of clinical trial (NPRM at §__.102(b)) should include additional explanation of what is encompassed by the term behavioral health-related outcomes.

2. Changes to the Assurance Process (NPRM at §§__.103 and __.108; current Rule at §__.103)

a. NPRM Goal

There has been concern expressed by some, such as SACHRP, that the current assurance process may be unduly burdensome for institutions and does not provide meaningful protections for human subjects. The changes proposed to the assurance process are intended to reduce unnecessary administrative burdens.

b. Current Rule

Requirements at §__.103 delineate procedural requirements for institutions and IRBs to follow to comply with the Common Rule.

c. NPRM Proposals

A number of substantive and procedural modifications are proposed to §__.103 of the Common Rule. The NPRM proposes to move the IRB recordkeeping requirements from §__.103(b)(4) and (5) of the Common Rule. They are now described in the NPRM in §__.108(a)(3) and (4), which pertains to IRB functions and operations

Additionally, the NPRM proposes to eliminate the current Common Rule requirement at §__.103(b)(1) that an institution provide a statement of ethical principles with which an institution will abide as part of the assurance process. This change was made because this provision is generally not enforced. Further, for international institutions that may receive U.S. government funding for research activities, it creates the impression that these international institutions must modify their internal procedures to comport with the set of principles designated on the FWA for activities conducted at those institutions that receive no U.S. government funding. OHRP specifically has received many questions about the extent to which international institutions must adhere to the ethical principles designated as part of the assurance process in research activities conducted by the institution that receive no Common Rule

department or agency funding. In order to provide clarity to these international institutions that such measures are not required, the NPRM proposes to delete the requirement at §__.103(b)(1).

The NPRM also proposes to eliminate the requirement in §__.103(b)(2) that an institution designate one or more IRBs on its FWA established in accordance with the Common Rule. The requirement in the current Common Rule at §__.103(b)(2) that IRBs have sufficient meeting space and staff to support IRB reviews and recordkeeping requirements is found in the NPRM at §__.108(a)(1). Note that federal departments or agencies retain the ability to ask for information about which IRBs review research conducted at an institution as part of the assurance process, even if that requirement is not explicitly mandated in the regulations.

Additionally, the NPRM proposes to eliminate the current requirement in §__.103(b)(3) that an up-to-date list of the IRB members and their qualifications be included in an institution's assurance. Instead, proposed §§__.108(a)(2) and __.115(a)(5) require that an IRB or the institution prepare and maintain a current list of IRB members. This modification also eliminates the current requirement in §__.103(b)(3) that changes in IRB membership be reported to the department or agency head or to OHRP when the existence of an assurance approved by HHS for federalwide use is accepted. SACHRP recommended on March 28, 2008, that OHRP pursue harmonizing the Common Rule with FDA's human subjects protection regulations by eliminating the requirement to submit IRB membership lists. SACHRP members felt that submitting IRB membership lists and reporting all changes in IRB membership to OHRP added

little to the protection of human subjects and that eliminating these requirements therefore would reduce unnecessary administrative burdens on institutions and OHRP.[77]

Note that in implementing the NPRM an additional, non-regulatory change is planned to the assurance mechanism. The current option of "checking the box" on an FWA to extend HHS's (or other Common Rule supporting agencies') regulatory authority to studies conducted by an institution that do not receive federal support would be eliminated. Importantly, for research other than clinical trials, institutions could, if they so desired, continue for purposes of their own internal rules to voluntarily extend the regulations to all research conducted by the institution, but this voluntary extension would no longer be part of the assurance process and the research would not be subject to OHRP oversight. This change would be expected to have the beneficial effect of encouraging some institutions to explore a variety of new flexible approaches to overseeing low-risk research that is not funded by a Common Rule agency, thus furthering the goal of this NPRM to decrease inappropriate administrative burdens on such research.

In addition, the NPRM proposes to remove the provision found in the current Common Rule at §__.103(d) that a department or agency head's evaluation of an assurance will take into consideration the adequacy of the proposed IRB(s) designated under the assurance in light of the anticipated scope of the institution's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

[77] Secretary's Advisory Committee on Human Research Protections. (2008, September 18). SACHRP Letter to HHS Secretary. Retrieved from Office for Human Research Protections: http://www.hhs.gov/ohrp/sachrp/sachrpletter091808.html

To further strengthen the new provision at §__.101(a) giving Common Rule departments and agencies explicit authority to enforce compliance directly against IRBs that are not affiliated with an assured institution, language is proposed at §__.103(e) requiring each IRB, institution, or organization that has oversight responsibility for non-exempt research involving human subjects covered by this policy and conducted by another institution to have and follow procedures for documenting the institution's reliance on the unaffiliated IRB and the respective responsibilities of each entity for meeting the regulatory requirements of this policy. This is already a requirement under the terms of a FWA. Such agreements would have to be included as part of the IRB records, per a proposed requirement at §__.115(a)(10). This change is proposed to address concerns about OHRP's current practice of enforcing compliance with the Common Rule through the institutions that were engaged in human subjects research, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB.

Finally, the NPRM would eliminate the requirement in the current Common Rule at §__.103(f) that grant applications undergo IRB review and approval for the purposes of certification. The grant application is often outdated by the time the research study is submitted for IRB review and contains detailed information about the costs of a study, personnel, and administrative issues that go beyond the mission of the IRB to protect human subjects. Therefore, experience suggests that review and approval of the grant application is not a productive use of IRB time.

Note that each assured institution continues to have responsibility for ensuring that the IRBs upon which it relies are registered with OHRP and are appropriately constituted to review and approve the human subjects research, as required under §§__.107 and __.108.

In developing the NPRM proposals related to the assurance process, consideration was given to the 2014 SACHRP recommendation that the assurance of compliance required under §__.103 be provided through the grant-making or contract process, as one of multiple "Representations and Certifications" already made by institutions when they apply for federal grants, contracts or cooperative agreements.[78] SACHRP suggested that such a proposal may reduce administrative burden on IRB offices responsible for the FWA process without significantly diminishing the protection that these offices provide human subjects.

Ultimately, SACHRP's recommendation was not adopted as an NPRM proposal because of concerns regarding the impact that removal of the FWA process would have on the ability for Common Rule departments and agencies to determine their compliance authority in certain circumstances. As part of SACHRP's recommended change to the assurance process, it was envisioned that only the primary awardee of a grant or contract would be required to obtain an assurance, and that this assurance would be provided through the grant-making or contract process. Subawardees or subcontractors may also be engaged in human subjects research, which extends the funding Common Rule department's or agency's authority to such institutions. However, Common Rule departments or agencies may not be able to ascertain that such

[78] See Secretary's Advisory Committee on Human Research Protections (SACHRP). (2014, March 13). Final Recommendations on Assurances and Engagement. Retrieved from SACHRP's Meetings: http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-14/assurancesandengagementrecommendations.html

institutions are required to follow the Common Rule for such human subjects research at their institution in the absence of an assurance filed with a Common Rule department or agency (including OHRP). In addition, some institutions have over a thousand grants or contracts with Common Rule departments and agencies and therefore would have over a thousand assurances. Certain institutional changes (for example, changes in the signatory official or human protections administrator) will require assurances to be updated. Ensuring that assurances are appropriately updated and keeping track of these updates are likely to pose challenges to Common Rule departments or agencies.

d. What would change?

- The regulatory requirement that an institution identify a set of ethical principles on which an institution will rely in all research conducted at that institution, regardless of funding source for the activity, would be deleted.
- The regulatory requirement that a written assurance include a list of IRB members for each IRB designated under the assurance would be replaced by the requirement that a written assurance include a statement that, for each designated IRB, the institution, or when appropriate the IRB, prepares and maintains a current detailed list of the IRB members with information sufficient to describe each member's chief anticipated contributions to IRB deliberation and any employment or other relationship between each member and the institution.

- The regulatory requirement specifying that changes in IRB membership be reported to the department or agency head, or to OHRP when the existence of an HHS-approved assurance is accepted, would be deleted.
- The requirement would be deleted that a department or agency head's evaluation of an assurance take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.
- For non-exempt human subjects research that takes place at an institution in which IRB oversight is conducted by an IRB not affiliated with that institution, the institution and non-affiliated IRB must establish and follow written procedures that identify compliance responsibilities of each entity that are set forth in a written agreement between the institution and the IRB.

e. Question for Public Comment

88. Would protection to human subjects in research be enhanced if OHRP conducted routine periodic inspections to ensure that the membership of IRBs designated under FWAs satisfy the requirements of §__.107?

3. Department or Agency Discretion about Applicability of the Policy (NPRM at §__.101(c), (d), (i)) and Discretion Regarding Additional Requirements Imposed by the Conducting or Supporting Department or Agency (NPRM and current Rule at §__.124)

a. NPRM Goals

The goals of the NPRM revisions in these sections are to: (1) formally codify the general practice that the ethical standards articulated in the Belmont Report is the ethical standard that Common Rule departments or agencies will use in determining whether an activity is covered under this policy; and (2) ensure that when relevant, either the department or agency conducting or supporting an activity may require additional protections for human subjects.

b. Current Rule

The current Common Rule allows in §__.101(c), (d), (i) for Federal department or agency heads to determine which specific activities or classes of activities are covered by the rule.

c. NPRM Proposals

As described in section II.A.2 above, the NPRM proposes to exclude specific categories of low-risk research and non-research activities from the scope of the Common Rule in order to reduce regulatory burden. Of course, there will be cases that call for the exercise of careful judgment in determining whether activities are in an exclusion category, or whether they are within the scope of the Common Rule. The NPRM proposes to retain the Common Rule's current requirement that Federal department or agency heads retain final judgment about the coverage of particular research activities under the Common Rule (§__.101(c)) and proposes an additional clause that

Federal department or agency heads must exercise their authority consistent with the principles of the Belmont Report, in order to require these Federal department and agency heads to make these judgments in consideration of the ethical protection of human research subjects.

The NPRM also proposes at §__.101(d) that the agency may require additional protections for specific types of research supported or conducted by the agency or department; however advance public notice will be required when those additional requirements apply to entities outside of the Federal agency itself. This requirement is intended to promote harmonization between Federal agencies or departments, to the extent possible, and to ensure transparency between funding entities and the regulated community.

Finally, at §__.101(i) the NPRM proposes to amend the criteria for a department or agency waiving the applicability of some or all of the provisions of the policy, by stating that the waiver must be supported by an argument that the alternative procedures to be followed are consistent with the principles of the Belmont Report. Here again, the addition of this provision is to make explicit the ethical basis underpinning how waiver decisions have and must be considered.

New definitions of "Department or agency head" and "Federal department or agency" are provided at §__.102(c) and (d) in the NPRM to help clarify these requirements. The NPRM proposes in §__.102(d) adding a definition of "Federal department or agency" in order to avoid confusion as to whether this phrase encompasses Federal departments or agencies that do not follow the Common Rule, and to clarify that this phrase refers to the department or agency itself, not its bureaus, offices or divisions. This is consistent with HHS's historical interpretation of the

current Rule. To distinguish this from the definition of Department or agency head found in the current regulations at §___.102(a) (and found in the NPRM at §___.102(c)), the example of the Secretary of HHS has been inserted to provide clarity. In addition, the definition of "institution" has been changed at §__.102(f) in the NPRM to clarify that departments can be considered institutions for the purposes of this policy.

4. Research Covered by This Policy Conducted in Foreign Countries (NPRM at §__.101(h))

The current Common Rule at §__.101(h) articulates that when research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. The current provision provides the Declaration of Helsinki, as amended in 1989, as an example of internationally recognized ethical standards that a foreign country might use as its ethical base. In this situation, the current Common Rule provides that if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy.

The NPRM proposes to remove the specific example provided in this provision. A concern with providing a specific example of internationally recognized ethical document is that such a document is subject to change independent of HHS or other Common Rule agencies, and

therefore could be modified to contain provisions that are inconsistent with U.S. laws and regulations.

I. Effective and Compliance Dates of New Rule (NPRM at §__.101(k))

1. Effective Dates

It is anticipated that the effective date of the final rule will be one year after publication in the Federal Register. The compliance date of the new rules would also be one year from the publication of the Final Rule, with two exceptions discussed below. However, a provision that is anticipated to provide additional regulatory flexibility to institutions or investigators could voluntarily be implemented 90 days from the publication of the Final Rule. This 90-day delay would give the Common Rule departments and agencies time to develop the documents and tools needed to assist institutions in implementing some of these provisions (e.g., the Secretary's broad consent template, and privacy safeguards under §__.105). The provisions that would provide additional regulatory flexibility include:

- the proposed exclusions in §__.101(b);
- the proposed exemptions in §__.104(d), (e) and (f);
- the proposal to no longer require IRB review of grant applications (§__.103(f) in the current Common Rule);

- the proposal to eliminate the regulatory requirement in §__.103 specifying that changes in IRB membership be reported to the department or agency head, or to OHRP when an HHS-approved assurance is approved;
- the proposed provision in §__.109(f) to eliminate the continuing review requirement for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing data or involve only observational follow up in conjunction with standard clinical care;
- the proposed provision in §__.116(g) stating that an IRB may approve a research proposal in which investigators obtain identifiable private information without individuals' informed consent for the purpose of screening, recruiting, or determining the eligibility of prospective human subjects of research, through oral or written communication or by accessing records, in order to obtain informed consent, if the research proposal includes an assurance that the investigator will implement standards for protecting the information obtained in accordance with and to the extent required by the §__.105 privacy safeguards; and
- the new provision in §__.117(c)(1)(iii) allowing a waiver of the requirement for a signed consent form if the subjects are members of a distinct cultural group or community for whom signing documents is not the norm, the research presents no more than minimal risk of harm to subjects, and there is an appropriate alternative method for documenting that informed consent was obtained.

In two cases, institutions would have longer than one year to comply: (1) the proposal for the Common Rule to cover all biospecimens (§__.102(e) in the NPRM); and (2) the proposal in

§__.114(b)(1) regarding identifying a single IRB that would be responsible for the review of certain multi-institutional clinical trials. The compliance date for these requirements would be three years after the publication of the final rule to allow institutions the necessary time to develop institutional policies and procedures necessary to implement these provisions. Comment is sought about whether a different approach to phasing in these provisions would allow the regulated community to better implement the changes proposed in this NPRM. Additional possibilities discussed amongst the Common Rule agencies included providing smaller institutions more time to implement these two changes, and somehow incentivizing early compliance with these provisions.

Further, the extension of the regulations to clinical trials that are not directly funded by a Common Rule department or agency, but that are conducted at an institution that receives funding from a Common Rule department or agency for other human subjects research, would not apply to an institution until the institution received federal funding for non-exempt research in an award made after the effective date of the final rule.

2. Transition Provisions

The ANPRM suggested that any change related to the extent to which biospecimens are covered under the Common Rule would only apply to biospecimens collected after the effective date of the revised Common Rule. Commenters noted concerns about imposing consent requirements on the use of biospecimens already collected—that is, not grandfathering in such resources—especially if these biospecimens are non-identified. Requiring that consent be obtained for the

use of these materials could result in their being rendered useless for research, which would represent a cost of its own in terms of lost opportunity. This concern was based on the practical limitations involved in obtaining consent for biospecimens that were de-identified in the past, given that it may not be possible to re-contact the original source.

a. Research Initiated Prior to the Effective Date of This Subpart (NPRM at §__.101(k)(1))

The NPRM addresses the transition provisions for human subjects research (as defined in the NPRM) initiated before the effective date of the policy. Ongoing human subjects research initiated prior to the effective date of the final rule may choose to comply with the provisions that provide additional regulatory flexibility discussed above, but would not need to comply with additional requirements related to:

- Coverage of clinical trials (§__.101(a)(2));
- Written procedures for documenting an institution's reliance on an unaffiliated IRB (§__.103(e));
- New exempt research categories and determination requirements (§__.104(c)-(f));
- Information and biospecimen protection requirements (§__.105);
- New IRB roster and written procedural requirements (§__.108(a)(2));
- Continuing review requirements (§__.109(f)(2));
- Additional IRB approval criteria for information safeguards and return of results plans (§__.111(a)(7) and (8));

- Requirements for cooperative research (§__.114);
- IRB recordkeeping requirements for documenting an institution's reliance on an unaffiliated IRB and exemption determinations (§__.115(a)(10) and (11)); and
- Requirements for obtaining and documenting informed consent (§§ __.116 and __.117) that become effective on the date of the final rule.

b. Use of Prior Collections of Biospecimens (NPRM at §__.101(k)(2))

Research involving the use of prior collections of biospecimens is permitted if the biospecimens were collected for either research or non-research purposes before the effective date of this subpart, and research use of the biospecimens occurs only after removal of any individually identifiable information associated with the biospecimens.

If prior collections of biospecimens are not individually identifiable, research using such non-identified biospecimens would continue to be not covered by the regulations even after the effective date of this policy.

Similarly, if prior collections of biospecimens are being stored or maintained in an individually identifiable form, but identifiers are removed from the biospecimens before being obtained by an investigator, the investigator's use of such nonidentifiable biospecimens would continue to be not covered by the regulations even after the effective date of this policy.

III. Regulatory Impact Analyses

A. Introduction

HHS has examined the impacts of this proposed rule under Executive Order 12866 on Regulatory Planning and Review (September 30, 1993); Executive Order 13563 on Improving Regulation and Regulatory Review (January 18, 2011); the Regulatory Flexibility Act of 1980, Pub. L. 96-354 (September 19, 1980); the Unfunded Mandates Reform Act of 1995, Pub. L. 104-4, (March 22, 1995); and Executive Order 13132 on Federalism (August 4, 1999).

Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects; distributive impacts; and equity). Executive Order 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in Executive Order 12866. HHS expects that this proposed rule would have an annual effect on the economy of $100 million or more in any one year and therefore is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act (RFA) requires agencies that issue a regulation to analyze options for regulatory relief of small businesses if a rule has a significant impact on a substantial number of small entities.[79] The RFA generally defines a "small entity" as (1) a proprietary firm meeting the size standards of the Small Business Administration (SBA); (2) a nonprofit organization that

[79] 5 U.S.C. 603

is not dominant in its field; or (3) a small government jurisdiction with a population of less than 50,000 (states and individuals are not included in the definition of "small entity").[80] HHS considers a rule to have a significant economic impact on a substantial number of small entities if at least 5 percent of small entities experience an impact of more than 3 percent of revenue. HHS anticipates that the proposed rule would not have a significant economic impact on a substantial number of small entities. Supporting analysis is provided in section III.G below.

Section 202(a) of the Unfunded Mandates Reform Act of 1995[81] requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) implicit price deflator for the gross domestic product. HHS expects this proposed rule to result in expenditures that would exceed this amount.

Executive Order 13132 establishes certain requirements that an agency must meet when it promulgates a rule that imposes substantial direct requirement costs on state and local governments or has federalism implications. HHS has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. The proposed changes in the rule

[80] 5 U.S.C. 601
[81] 2 U.S.C. 1532

represent the Federal Government regulating its own program. Accordingly, HHS concludes that the proposed rule does not contain policies that have federalism implications as defined in Executive Order 13132 and, consequently, a federalism summary impact statement is not required.

B. Summary of the Proposed Rule

This NPRM is being issued to propose revisions to modernize, strengthen, and make more effective the current regulations for protecting human subjects. This proposed rule enhances clarity and transparency of the consent process by imposing stricter new requirements regarding the information that must be given to prospective subjects including the elements of consent in a variety of circumstances. It will also allow consent to the secondary research use of biospecimens and identifiable private information, given specific conditions are met. Enhanced protections to subjects are also achieved through greater transparency by posting of informed consent forms used in clinical trials. Several proposed changes (such as explicitly excluding certain activities from the rule, expanding the categories of research exempt from some of the requirements of the proposed rule, and eliminating continuing review by an IRB in some situations) would relieve the burden of unnecessary or unwarranted stringent review of some low-risk studies that do not pose threats to the welfare of subjects. Other proposed changes expand the reach of the regulations by covering all clinical trials, regardless of funding source, and by changing the definition of human subject to include research in which an investigator uses, studies, or analyzes a biospecimen. Single IRB review for multi-institutional studies would also be generally required, except where local IRB review is required by law, to reduce

duplicative IRB reviews. Still other revisions clarify or revise requirements for and responsibilities of IRB review and documentation. New exempt categories are proposed, requiring that investigators and institutions comply with minimum standards for protecting privacy. A new process is also proposed through which investigators may input information about a prospective study into a tool in order for that tool to generate exemption determinations.

1. Accounting Table

Table 1 summarizes the quantified and non-quantified benefits and costs of all proposed changes to the Common Rule. Over the 2016-2025 period, present value benefits of $2,629 million and annualized benefits of $308 million are estimated using a 3 percent discount rate; present value benefits of $2,047 million and annualized benefits of $291 million are estimated using a 7 percent discount rate. Present value costs of $13,342 million and annualized costs of $1,564 million are estimated using a 3 percent discount rate; present value costs of $9,605 million and annualized costs of $1,367 million are estimated using a 7 percent discount rate. Non-quantified benefits include improved human subjects protections in clinical trials and biospecimen research not currently subject to oversight; enhanced oversight of research reviewed by unaffiliated IRBs; increased uniformity in regulatory requirements among Common Rule agencies; standardization of human subjects protections when variation among review IRBs is not warranted; revised informed consent forms and processes; improved protection of biospecimens and identifiable private information; and increased transparency of Common Rule agency-supported clinical trials to inform the development of new consent forms. Non-quantified costs include the time needed for consultation among Common Rule agencies before federal guidance is issued; and the

time needed by investigators to obtain, document, and track the permissible uses of biospecimens and identifiable private information for secondary research use.

Table 1. Accounting Table of Benefits and Costs of All Proposed Changes

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits	2,629	2,047	308	291
Non-quantified Benefits Improved human subjects protections in clinical trials and biospecimen research not currently subject to oversight; enhanced oversight in research reviewed by unaffiliated IRBs; increased uniformity in regulatory requirements among Common Rule agencies; ethical benefit of respecting an individual's wishes in how his or her biospecimens are used in future research; standardization of human subjects protections when variation among review IRBs is not warranted; improved informed consent forms and processes; improved protection of biospecimens and identifiable private information; better ensuring availability of biospecimens for future research activities; and increased transparency of Common Rule-supported clinical trials to inform the development of new consent forms.				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs	13,342	9,605	1,564	1,367
Non-quantified Costs Time for consultation among Common Rule agencies before federal guidance is issued; time for investigators to obtain consent for secondary use of biospecimens or identifiable private information.				

Table 2 summarizes the quantified present value benefits and costs of each proposed change to the Common Rule using a 3 percent discount rate.

Table 2. Accounting Table of Quantified Benefits and Costs of Each Proposed Change

Proposed Change	Present Value of 10 Years at a 3 Percent Discount Rate (Millions of 2013 Dollars)	
	Benefits	**Costs**
Costs to Learn New Requirements and Develop Training Materials; OHRP Costs to Develop Training and Guidance Materials, and To Implement the Rule	-	208
Extending Oversight to IRBs Unaffiliated With an Institution Holding an FWA	-	84.6
Extending Common Rule Compliance Oversight to Clinical Trials Regardless of Funding Source	-	18.3
Excluding Activities from the Requirements of the Common Rule because They are not Research	74.0	-
Excluding Low-Risk Research from the Requirements of the Common Rule	740	-
Clarifying and Harmonizing Regulatory Requirements and Agency Guidance	-	-
Expanding the Definition of Human Subject to Include Research involving Non-Identified Biospecimens and Creating an Exemption for Secondary Research Using Biospecimens or Identifiable Private Information	-	101
Modifying the Assurance Requirements	5.81	-
Requirement for Written Procedures and Agreements for Reliance on External IRBs	-	11.3
Eliminating the Requirement that the Grant Application Undergo IRB Review and Approval	310	-
Tracking and Documenting Exemption Determinations	-	-
Amending the Research and Demonstration Project Exemption	37.0	0.36
Expansion of Research Activities Exempt from IRB Review	70.0	-

Table 2. Accounting Table of Quantified Benefits and Costs of Each Proposed Change

Proposed Change	Present Value of 10 Years at a 3 Percent Discount Rate (Millions of 2013 Dollars)	
	Benefits	**Costs**
Exemption for the Storage and Maintenance of Biospecimens and Identifiable Private Information for Future, Unspecified Secondary Research Activities after Consent has been Sought and Obtained	-	1.58
Protection of Information and Biospecimens	-	457
Elimination of Continuing Review of Research Under Specific Conditions	145	38.8
Amending the Expedited Review Procedures	16.8	2.71
Revised Criteria for IRB Approval of Research	126	0.07
Cooperative Research	1,103	155
Changes in the Basic Elements of Consent, Including Documentation	-	4.55
Obtaining Consent to Secondary Use of Biospecimens and Identifiable Private Information	-	12,245
Elimination of Requirement to Waive Consent in Certain Subject Recruitment Activities	1.21	-
Requirement for Posting of Consent Forms for Clinical Trials supported by Common Rule Department or Agencies	-	14.6
Alteration in Waiver for Documentation of Informed Consent in Certain Circumstances	-	-

C. Need for the Proposed Rule

Federal regulations governing the protection of human subjects in research have been in place for more than three decades, and 20 years have passed since the Common Rule was adopted by 15 Federal departments and agencies[82] in an effort to promote uniformity, understanding, and compliance with human subject protections. Today 18 departments and agencies have adopted the rule.[83] As such, compliance with the Common Rule is a condition for receiving federal funding from one of these agencies. Note that an additional agency (Department of Labor) is joining this proposed rulemaking in order to promulgate the Common Rule in DOL regulations and to apply the regulations to human subjects research that DOL may conduct or support, pending the scope of the final rule. Although professional organizations have codes of conduct and guidelines for members conducting research, only the Federal government has the authority to regulate the activities of institutions using public funds for human subjects research. Since the Common Rule was developed, the volume of research has increased, evolved, and diversified. Although the regulations have been amended over the years, the enterprise has changed to the point that the current regulations might be outdated in some important ways.

Under the current system, the regulated community notes that limited IRB resources are often diverted away from focusing on higher-risk studies because of the considerable time spent reviewing low-risk and minimal-risk research. Theoretically, this can result in inadequate attention devoted to research that could seriously harm subjects and unnecessary delay of very

[82] The current 15 Common Rule signatory agencies are: Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Consumer Product Safety Commission; Agency for International Development; Department of Housing and Urban Development; Department of Justice; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; and Department of Transportation.
[83] In addition to the signatory Common Rule departments and agencies, three departments and agencies have not issued the Common Rule but currently apply 45 CFR Part 46: The Central Intelligence Agency, the Social Security Administration, and the Department of Homeland Security.

low-risk research. From the perspective of human subjects participating in research, the length and complexity of consent forms has been increasing even for relatively low-risk studies, hindering subject understanding of the research activities in which they participate. Current and prospective research subjects have increasingly indicated that they would like to be asked about the future research use of their biospecimens. This desire is not necessarily based on concern of inappropriate disclosure or use of personally identifiable private information generated from the biospecimen, but rather is rooted in the sense that subjects should, whenever possible, be asked about such future research use. Finally, the current system contains some oversight gaps that should be addressed to ensure that the system is covering the riskiest studies and that should compliance-related issues occur, the IRBs responsible for these issues may be held responsible. Provisions are needed to ensure the Rule's consistency with the principles of Belmont Report and to protect privacy in the context of increasing cybercrime and the introduction of modern research methods that may jeopardize subject privacy while not unnecessarily slowing research.

Thus, this NPRM proposes a number of measures to address the issues described above. Provisions that strengthen the requirements for informed consent and promote transparency in the informed consent process include: (1) requiring that the informed consent form be designed and presented in such a way that facilitates a prospective subject's understanding of why one would want to participate in a research study or not; (2) requiring that the informed consent form present the required information before providing any other information to a prospective subject; (3) revising and adding to the required elements of consent; (4) requiring for certain clinical trials the posting of a copy of at least one version of a consent form on a publicly available federal website; and (5) changing the conditions and requirements for waiver or alteration of

consent to remove ambiguity, including a new provision that under specific conditions an IRB may approve a research proposal in which investigators obtain identifiable private information without individuals' informed consent for the purpose of screening, recruiting, or determining eligibility of prospective human subjects of research.

Provisions that strengthen humans subjects protections include: (1) a provision that would hold IRBs not affiliated with engaged institutions directly responsible for compliance; (2) extending the scope of the policy to research most likely to involve greater-than-minimal risk, that is, clinical trials; and (3) creating standard privacy safeguards for biospecimens and information.

Provisions that strengthen the extent to which the ethics system promotes the principle of respect for persons: (1) requiring informed consent for most research activities involving biospecimens, regardless of identifiability; (2) allowing for waiver of informed consent in research activities involving biospecimens only in rare circumstances; and (3) adding a provision that would prohibit waiver of consent if someone has been asked to provide their broad consent for future research use of their biospecimens or identified private information, and that person refuses to give such consent.

New provisions that would allow IRBs greater flexibility to focus resources on higher-risk research include: (1) distinguishing categories of activities that would be excluded from the rule; and (2) expanding and clarifying categories of exempt research. Provisions that streamline or reduce burden for IRBs or institutions include: (1) requiring consultation among the Common Rule agencies for the purpose of harmonizing guidance; (2) eliminating an administrative

requirement for reporting IRB rosters; (3) removing the requirement that IRBs must review and approve grant applications; (4) eliminating under certain specific circumstances, continuing review for minimal risk studies that undergo expedited review; (5) clarifying when expedited review can occur; and (6) mandating use of a single IRB for multi-institutional studies.

D. Analysis of Benefits and Costs

In this section, the analysis of the quantified and non-quantified benefits and costs of the proposed changes to the Common Rule are presented. First, the common assumptions of the analysis are discussed. Then, this section presents the estimated quantified and non-quantified benefits and costs of the specific changes. Because of the lack of available data about IRB effectiveness and how IRBs function operationally[84], many of the estimations in this analysis are based on anecdotal evidence. On all assumptions and estimates presented below, public comment is requested on the accuracy of these assumptions and on whether better data sources are available to support the analysis.

1. Analytic Assumptions

The analysis relies on common data elements and assumptions, detailed below, concerning the domestic entities, individuals, and IRB reviews affected by the proposed changes to the Common Rule. Many of the estimates are derived from a 1998 NIH-sponsored evaluation of the implementation of Section 491 of the Public Health Service Act, which involved nationally

[84] See, e.g.,, L Abbott and C. Grady, A Systematic Review of the Empirical Literature Evaluating IRBs: What We Know and What We Still Need to Learn. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3235475/.

representative surveys of IRBs, institutions, and investigators. Based on a review of the literature, this study contains the best available data on the time spent on protocol reviews as well as the characteristics of the reviews themselves. As previously stated, public comment is requested on these and other estimates used throughout the analysis.

According to the OHRP database of registered institutions and IRBs, there are approximately 8,035 institutions with a FWA, of which 2,871 have an IRB. Some institutions have multiple IRBs and some IRBs are not affiliated with an institution with an FWA, for a total of 3,499 IRBs.

The OHRP database of registered institutions and IRBs shows that there are 675,390 annual reviews of non-exempt protocols involving human subjects. It is estimated that there are 324,187 initial protocol reviews (48 percent) and 351,203 continuing protocol reviews (52 percent) based on estimates reported in Bell et al.[85] In each category, it is estimated that 69 percent of these reviews are convened and 31 percent are expedited based on estimates reported in Bell et al. It is estimated that there are 472,773 reviews of single-site protocols (70 percent) and 202,617 reviews of multi-site protocols (30 percent) based on estimates reported in Bell et al. This analysis also assumes that there are on average 5 IRB reviews per multiple-site protocol. This implies that there are 472,773 single-site protocols and 40,523 multi-site protocols, for a total of 513,296 protocols. The above implies that there are approximately 246,382 new protocols each year.

[85] Bell J, Whiton J, and Connelly S, Final Report: Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects, 1998.

Based on queries of ClinicalTrials.gov, it is estimated that HHS supports 909 new clinical trials annually, of which 575 are regulated by FDA. In addition, it is estimated that there are 1,399 clinical trials currently not subject to oversight by either the Common Rule or FDA regulations. Finally, based on queries of ClinicalTrials.gov, Common Rule agencies support approximately 5,270 studies total.

Many individuals in various occupations would be affected by the proposed changes to the Common Rule. It is estimated that an average of one institution official at each institution with an FWA would be affected by these changes, for a total of 2,871 institution officials. The OHRP database of registered institutions and IRBs shows that there are 10,197 full-time equivalents (FTEs) staff persons at IRBs working as administrators or administrative staff, and that 89.8 percent of IRBs have an administrator. It is assumed that these individuals work full-time, implying a total of 3,193 IRB administrators and 7,004 IRB administrative staff. The OHRP database of IRB rosters contains 3,359 individuals who serve as IRB chairs and an additional 32,518 voting members. The number of IRB chairs is less than the number of IRBs because some individuals chair multiple IRBs. It is assumed that there are 439,968 investigators who conduct human subjects research in the United States.[86]

The hourly wages of individuals affected by the proposed changes to the Common Rule is estimated using information on annual salaries provided by the U.S. Bureau of Labor Statistics and the U.S. Office of Personal Management. The salary of postsecondary education

[86] To derive this estimate, the number of new protocols, estimated above, is divided by the average number of new protocols submissions reported per investigator. This is estimated to be 2.8 based on Bell et al. This number is then multiplied by the average number of investigators working on each protocol (which is assumed to be 5). This allows for an accounting of investigators working on multiple protocols as well as protocols with multiple investigators.

administrators is used as a proxy for the salary of institution officials; the salary of lawyers is used as a proxy for the salary of institution legal staff and IRB administrators; the salary of office and administrative support workers is used as a proxy for the salary of IRB administrative staff; the salary of postsecondary health teachers is used as a proxy for the salary of IRB chairs and IRB voting members; the salary of postsecondary teachers is used as a proxy for the salary of investigators; the salary of database and systems administrators and network architects is used as a proxy for the salary of database administrators; and the salary of all occupations, as a proxy for the salary of prospective human subjects. The federal employees affected by the proposed changes to the Common Rule are assumed to be Step 5 within their GS-level and earn locality pay for the District of Columbia, Baltimore, and Northern Virginia. Annual salaries are divided by 2,087 hours to derive hourly wages. To project wages over 2016-2025, wages are adjusted for growth over time using the average annual per capita growth in real wage income over 1929-2012 reported by the U.S. Bureau of Economic Analysis, which is 2.1 percent. The total dollar value of labor, which includes wages, benefits, and overhead, is assumed to be equal to 200 percent of the wage rate.

The RIA calculates person-hours by occupation per initial protocol review and per continuing protocol review based on each occupation's share of total person-hours reported in Bell et al. In particular, Bell et al. reports that institution officials account for 4 percent, IRB administrators account for 28 percent, IRB administrative staff account for 30 percent, IRB chairs account for 7 percent, and IRB voting members account for 31 percent of total person-hours. The RIA assumes that the average number of person-hours spent per review equals the weighted average of the

person-hours spent per convened review and the person-hours spent per expedited review. It is further assumed that convened review requires twice as many person-hours as expedited review.

Table 3 shows the number of entities affected by the proposed changes to the Common Rule and other common assumptions of the analysis (described above).

Table 3. Number of Affected Entities and Other Common Assumptions

Description	Estimate
U.S. Institutions and IRBs	
Institutions with a Federalwide Assurance	8,035
Institutions with an IRB	2,871
Institutions without an IRB	5,164
IRBs	3,499
Occupations	
Institution officials	2,871
IRB administrators	3,193
IRB administrative staff	7,004
IRB chairs	3,359
IRB voting members	32,518
Investigators	439,968
Hourly Wages	
Institution officials (2013)	$48.20
Institution legal staff (2013)	$63.24
IRB administrators (2013)	$63.24

Table 3. Number of Affected Entities and Other Common Assumptions

Description	Estimate
IRB administrative staff (2013)	$16.72
IRB chairs (2013)	$46.36
IRB voting members (2013)	$46.36
Investigators (2013)	$35.75
Database administrators (2013)	$38.69
Prospective Human Subjects (2013)	$22.25
Federal employees in the District of Columbia, Baltimore, and Northern Virginia (2013)	
GS-9 Step 5	$28.04
GS-13 Step 5	$48.35
GS-14 Step 5	$57.13
GS-15 Step 5	$67.21
Average annual per capita growth in real wage income	2.1%
IRB Reviews of Human Subjects Research Protocols at U.S. Institutions	
Annual reviews of non-exempt protocols	675,390
Initial protocol reviews (48%)	324,187
Convened reviews (69%)	223,689
Expedited reviews (31%)	100,498
Continuing protocol reviews (52%)	351,203
Convened reviews (69%)	242,330
Expedited reviews (31%)	108,873
Annual reviews of single-site protocols (70%)	472,773
Annual reviews of multi-site protocols (30%)	202,617
Human Subjects Research Protocols at U.S. Institutions	
Active protocols	513,296

Table 3. Number of Affected Entities and Other Common Assumptions

Description	Estimate
Single-site protocols	472,773
Multi-site protocols	40,523
New protocols (48%)	246,382
Average number of IRB reviews per active multi-site protocol	5
Clinical Trials	
New clinical trials supported by HHS annually	909
Regulated by FDA	575
Active clinical trials currently not regulated by the Common Rule or FDA regulations	1,399
Clinical Trials supported by Common Rule Agencies	5,270
Person-Hours per Protocol Reviewed by Occupation and Type of Review	
Institution officials	
Initial protocol reviews	
Convened reviews	0.52
Expedited reviews	0.26
Continuing protocol reviews	
Convened reviews	0.10
Expedited reviews	0.05
IRB administrators	
Initial protocol reviews	
Convened reviews	3.64
Expedited reviews	1.82
Continuing protocol reviews	
Convened reviews	0.68
Expedited reviews	0.34

Table 3. Number of Affected Entities and Other Common Assumptions

Description	Estimate
IRB administrative staff	
Initial protocol reviews	
Convened reviews	3.91
Expedited reviews	1.95
Continuing protocol reviews	
Convened reviews	0.73
Expedited reviews	0.36
IRB chairs	
Initial protocol reviews	
Convened reviews	0.91
Expedited reviews	0.46
Continuing protocol reviews	
Convened reviews	0.17
Expedited reviews	0.08
IRB voting members	
Initial protocol reviews	
Convened reviews	2.70
Expedited reviews	1.35
Exempt reviews	0.50
Continuing protocol reviews	
Convened reviews	0.75
Expedited reviews	0.38
Investigators	
Initial protocol reviews	

Table 3. Number of Affected Entities and Other Common Assumptions

Description	Estimate
Convened reviews	13.65
Expedited reviews	7.15
Exempt reviews	0.50
Continuing protocol reviews	
Convened reviews	6.83
Expedited reviews	3.58

2. Analysis of Proposed Changes

Presented below is an analysis of the quantified and non-quantified benefits and costs of the proposed changes to the Common Rule. For each proposed change, we describe and explain the need for the change, provide a qualitative summary of the anticipated benefits and costs, describe the methods we use to quantify benefits and costs, and then present estimates.

a. Costs for the Regulated Community to Learn New Requirements and Develop Training Materials; Costs for OHRP to Develop Materials and Guidance

Domestic institutions, IRBs, and investigators would need to spend time learning the proposed changes to the Common Rule once training materials become available to them. In addition, IRBs and OHRP would need to update training materials for investigators. Finally, OHRP would need to develop guidance, templates, lists, and a number of electronic resources (as stated in the NPRM).

The RIA estimates that institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators would each spend 5 hours to learn the proposed changes to the Common Rule. It is also estimated that institution officials would spend two hours to learn new procedures, IRB administrators would spend 20 hours, and administrative staff would spend 80 hours. Based on the estimates presented in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016 wages and adjusting for overhead and benefits. For example, to calculate the dollar value of time spent by institution officials to learn the proposed changes to the Common Rule in 2016, we multiply the number of institution officials (2,871) by the number of hours spent per institutional official (5), by the projected hourly wage of institution officials ($48.20), and by the adjustment factor for benefits and overhead (2).

In order to develop the resources required by the NPRM, it is anticipated that OHRP would need:

- Three staff people at the GS-14 level to: (1) promote harmonization efforts to issue guidance across Common Rule agencies and departments; (2) develop a number of "Secretary's Lists" (akin to guidance documents) referenced in the rule that would be periodically reviewed and revised; (3) develop template agreements/ contracts for use by the regulated community; (4) manage the administrative transition to the new processes proposed in the NPRM; and, (5) develop the language and technical requirements for a web-based tool that would allow investigators (and others) to determine if a project fits into a category of research exempt from certain regulatory requirements.

- One staff person at the GS-13 level to manage process changes proposed in the NPRM, and assist with implementation for the web-based tools and portals proposed.
- One staff person at the GS-9 level to provide technical support for the web-based portals proposed in the NPRM.

In addition, the first year after a final rule is published staffing resources beyond what is described above would be necessary:

- Three staff people at the GS-14 level to draft new guidance and revise old guidance.
- One staff person at the GS-14 level to conduct educational seminars.

OHRP also anticipates the following in non-personnel costs:

- Technical development of a web-based tool that investigators (and others) may use to determine if a project fits into a category of research that is exempt from certain regulatory requirements ($350,000)
- Technical development of two web-based portals for investigators to post final consent forms for HHS-funded clinical trials, and for investigators that conduct certain types of demonstration projects to post information about said projects ($200,000)
- Developing five educational seminars (including travel) to educate the public about the requirements of the new rule ($200,000)
- Upgrading equipment for education activities ($50,000)

Present value costs of $208 million and annualized costs of $24.3 million are estimated using a 3 percent discount rate; present value costs of $199 million and annualized costs of $28.3 million are estimated using a 7 percent discount rate. Table 4 summarizes the quantified and non-quantified benefits and costs to learn new requirements and develop training materials.

Table 4. Summary of Estimated Benefits and Costs to Learn New Requirements and Develop Training Materials

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits None (although benefits discussed in association with other provisions would be impossible without this activity)				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time and money to learn new requirements, update training materials, and develop tools	208	199	24.3	28.3
Non-quantified Costs None				

b. Extending Oversight to IRBs Unaffiliated with an Institution Holding a Federalwide Assurance (NPRM at §__.101(a))

The NPRM proposes a change to place unaffiliated IRBs within the realm of entities to which the policy applies. This new provision gives Common Rule departments and agencies explicit authority to enforce compliance directly against IRBs that are not affiliated with an assured institution. This change addresses concerns about OHRP's current practice of enforcing compliance with the Common Rule through the institutions that were engaged in human subjects research, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB. This change should encourage institutions to more willingly rely on qualified unaffiliated IRBs for cooperative research, as is required under the proposed changes at §__.114 (see section III.D.2.s of this RIA below).

The OHRP database of assured institutions and registered IRBs shows that there are approximately 449 IRBs not affiliated with an institution holding an FWA that would now be subject to oversight. These IRBs would develop an estimated average of 10 written agreements with other institutions each year as a result of this proposal. It is further estimated that each agreement would require an average of 10 hours of institution legal staff time and 5 hours of IRB administrator time to complete.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value costs of $84.6 million and annualized costs of $9.93 million are estimated using a 3 percent discount rate; present value costs of $69.2 million and annualized costs of $9.86 million are estimated using a 7 percent discount rate. Table 5 summarizes the quantified and non-quantified benefits and costs of extending oversight to IRBs unaffiliated with an institution holding an FWA.

Table 5. Summary of Estimated Benefits and Costs of Extending Oversight to IRBs Unaffiliated with an Institution Holding an Federalwide Assurance (NPRM at §__.101(a))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Encouragement to institutions to rely on unaffiliated IRBs when appropriate.				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Developing IRB authorization agreements	84.6	69.2	9.93	9.86
Non-quantified Costs None				

c. Extending Common Rule Compliance Oversight to Clinical Trials Regardless of Funding Source (NPRM at §__.101(a)(2))

The proposed rule would extend the regulations to cover clinical trials conducted at an institution in the United States that receives federal support from a Common Rule department or agency for non-exempt, non-excluded human subjects research, regardless of the funding source of the specific clinical trial. Extension of the rules would not apply to clinical trials already regulated by FDA.

A small percentage of clinical trials currently are not subject to oversight by either the Common Rule or FDA regulations. This change in policy gives OHRP the authority to conduct oversight compliance of clinical trials not otherwise subject to human subjects protection regulations. The benefits to be gained in terms of equitable and just distribution of protections to all subjects of clinical trials warrant closing this gap in the current system. Moreover, while it is expected that this extension would apply to only a small percentage of clinical trials, they are the type of studies that often pose the greatest risks to subjects. Since this extension is expected to bring research that poses the most risk to research subjects under the rules, it is presumed that the current option in the FWA that allows institutions to voluntarily extend the funding Common Rule department or agency's compliance oversight authority to all research conducted at an institution regardless of funding source (i.e., "checking the box") would be unnecessary.

Although more research would be covered by the policy, the extension is contingent on an entity receiving federal support for non-exempt human subjects research; thus, the entity already should have an established IRB in place and would not incur costs establishing one or contracting with an unaffiliated IRB.

The RIA estimates that there are 1,399 clinical trials currently not subject to oversight by either the Common Rule or FDA regulations. It is estimated that in 2016 all 1,399 of these clinical trials would undergo convened initial review. In subsequent years, an estimated 672 protocols would undergo convened initial review, 502 would undergo convened continuing review, and 225 would undergo expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value costs of $18.3 million and annualized costs of $2.15 million are estimated using a 3 percent discount rate; present value costs of $15.1 million and annualized costs of $2.15 million are estimated using a 7 percent discount rate. Table 6 summarizes the quantified and non-quantified benefits and costs of oversight for clinical trials currently not subject to oversight.

Table 6. Summary of Estimated Benefits and Costs of Extending Common Rule Compliance Oversight for Clinical Trials Regardless of Funding Source (NPRM at §__.101(a)(2))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)	**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**

BENEFITS	3 Percent	7 Percent	3 Percent	7 Percent
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Improving institutional willingness to use unaffiliated IRBS, thereby facilitating the implementation of the proposed changes to §__.114 (Cooperative Research).				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Increase in number of reviews	18.3	15.1	2.15	2.15
Non-quantified Costs None				

d. Activities Excluded from the Requirements of the Common Rule because They Are Not Research (NPRM at §__.101(b)(1))

Six categories of activities would be excluded from the regulatory requirements of the Common Rule because they are not considered research as defined in §__.102(l) in the NPRM: (1) certain data collection and analysis activities conducted for an institution's own internal operation and program improvement purposes; (2) certain activities that focus directly on the specific individuals about whom the information is collected (i.e., oral history, journalism, biography, and historical scholarship); (3) certain collection and analysis activities conducted by a criminal justice agency solely for criminal justice investigative purposes; (4) certain quality assurance or improvement activities; (5) certain public health surveillance activities; and (6) certain activities conducted by a defense, national security, or homeland security authority. The proposal in the NPRM to explicitly list certain activities that are not considered "research" for the purposes of

this policy is not intended to suggest that these are the only six categories that may be considered not to meet the definition of "research."

Federal agencies (and some institutions in the regulated community) engaged in activities considered in these exclusions already interpret such activities as excluded from the regulations. Thus, in general, the exclusions found in proposed §__.101(b)(1) represent a proposed codification of current practice. However, comments to the ANPRM suggested that at many institutions, activities that would now be explicitly excluded from the policy are being routinely reviewed by IRBs. While many institutions are specifically creating policies to state that oral history or journalism activities do not require IRB review[87], institutions vary and some continue to require IRB review for other activities (such as quality improvement activities[88]) that may not meet the Common Rule's definition of research. Thus, explicitly excluding these six categories because they are to be considered not research would provide clarity to the regulatory community about what constitutes research per this policy, and also likely result in a modest decrease in the number of IRB reviews that occur each year in institutions.

Institutions, investigators, and IRBs involved in supporting, conducting, or reviewing these activities would no longer incur the costs of IRB review and approval and continuing review. Activities that were not intended to be subject to the regulations would clearly be excluded,

[87] See e.g., Schrag, ZM "Smithsonian Frees Oral History, Journalism, and Folklore," *Institutional Review Blog*, 30 July 2010, http://www.institutionalreviewblog.com/2010/07/smithsonian-frees-oral-history.html. See also "More Universities Deregulate Oral History", 7 April 2010, http://www.institutionalreviewblog.com/2010/04/more-universities-deregulate-oral.html.

[88] See e.g.,, Baily, MA "Quality Improvement Methods in Health Care," in From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns, ed. Mary Crowley (Garrison, NY: The Hastings Center, 2008), 147-152 http://www.thehastingscenter.org/Publications/BriefingBook/Detail.aspx?id=2204.

allowing such activities to proceed without delays caused by the need for IRB submission, review, and approval.

It is estimated that 6,754 annual reviews of protocols (1.0 percent) would no longer be conducted as a result of the exclusions proposed in §___.101(b)(1). Of these reviews, 2,237 would have undergone convened initial review, 1,005 would have undergone expedited initial review, 2,423 would have undergone convened continuing review, and 1,089 would have undergone expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $74.0 million and annualized benefits of $8.67 million are estimated using a 3 percent discount rate, and present value benefits of $60.5 million and annualized benefits of $8.61 million are estimated using a 7 percent discount rate. Table 7 summarizes the quantified and non-quantified benefits and costs of excluding these activities from the requirements of the Common Rule.

Table 7. Summary of Estimated Benefits and Costs of Excluding Activities from the Requirements of the Common Rule because they are not Research (NPRM at §__.101(b)(1))

	Present Value of 10 Years	**Annualized Value over 10 Years**

	by Discount Rate (Millions of 2013 Dollars)		by Discount Rate (Millions of 2013 Dollars)	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of reviews	74.0	60.5	8.67	8.31
Non-quantified Benefits Increased clarity in what must be reviewed; ability for IRBs to focus efforts on reviews of higher-risk, more complex, research activities				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

e. Low-risk Research Activities Excluded from the Requirements of the Common Rule because They Are Already Subject to Independent Controls (NPRM at §__.101(b)(2))

The NPRM proposes that four additional categories of research activities be explicitly excluded from the regulatory requirements of the Common Rule because they are low-risk and already subject to independent controls in the absence of the protections of the Common Rule. These are: (1) certain research activities that involve the use of certain educational tests, survey procedures, interview procedures, or observation of public behavior (a revised version of current exemption category 2); (2) certain research activities involving the collection or study of information (a revised version of current exemption category 4); (3) certain research activities conducted by a government agency using government-generated, non-research data; and (4)

certain data collection and analysis activities using identifiable health information subject to the HIPAA Privacy Rule.

The current Common Rule articulates two exemptions (current Rule at §___.101(b)(2) and (4)) that appear in a similar format in the proposed NPRM exclusions. Current Common Rule exemption category 2 is found in the NPRM in §__.101(b)(2)(i); current exemption category 4 is found in NPRM §___.101(b)(2)(ii). In addition to being considered excluded from the rule (rather than exempt from certain requirements of the rule), current exemption category 2 (NPRM §___.101(b)(2)(i)) has been clarified to state that interventions in conjunction with collection of data through the use of educational tests, survey procedures, interview procedures or observation of public behavior uninfluenced by the investigator (including visual or auditory recording) may not be used in research activities that qualify for this exclusion. For the research activities at issue in the NPRM at §___.101(b)(2)(i), it is presumed that the activities poses little to no risk to subjects, and that the subjects knowingly and willingly provide the information, or decline to participate. Thus, IRB review of the research and consent related documents are not believed to be necessary for such activities.

Four changes are proposed to current exemption category 4 (NPRM at §___.101(b)(2)(ii)). First, the provision would now be considered excluded from the rule, not just exempt from certain requirements of the rule. Second, the provision no longer includes pathological specimens or diagnostic specimens. Third, NPRM §___.101(b)(2)(ii) removes the word "existing" from the provisions. This is intended to clarify the scope of the exclusion to allow for information that will be collected in the future. Finally, a condition is added requiring that the exclusion may

only be used when the investigator has no plans to contact subjects, re-identify subject, or otherwise conduct an analysis that could lead to creating identifiable private information.

Neither the exclusion at NPRM §___.101(b)(2)(iii) (certain research activities conducted by a government agency using government-generated, non-research data) nor the exclusion at NPRM §___.101(b)(2)(iv) (certain data collection and analysis activities using identifiable health information subject to the HIPAA Privacy Rule) appear in the current Rule. These research activities are excluded because human subjects are independently protected through other mechanisms or laws. It is anticipated that the exclusion of activities regulated by HIPAA as health care operation activities, public health activities, or research (NPRM at §___.101(b)(2)(iv)) would represent a significant reduction in the volume of activities an IRB reviews. For example, the proposed exclusion at §___.101(b)(2)(iv) would mean that at institutions subject to the HIPAA regulations, projects where one is simply analyzing protected health information from medical charts would not be required to undergo IRB review.

Institutions, investigators, and IRBs involved in supporting, conducting, or reviewing these activities would no longer incur the costs of IRB review, approval, and continuing review. Activities that were not intended to be subject to the regulations would clearly be excluded, allowing such activities to proceed without delays caused by the need for IRB submission, review, and approval.

The RIA estimates that 67,539 annual reviews of protocols (10.0 percent) would no longer be conducted as a result of the proposed exclusions in §__.101(b)(2). It is anticipated that the

exclusion of certain activities covered by the HIPAA Privacy Rule would drive the estimated reduction in annual IRB reviews of protocols. Of these reviews, 22,369 would have undergone convened initial review, 10,050 would have undergone expedited initial review, 24,233 would have undergone convened continuing review, and 10,887 would have undergone expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $740 million and annualized benefits of $86.7 million are estimated using a 3 percent discount rate, and present value benefits of $605 million and annualized benefits of $86.1 million are estimated using a 7 percent discount rate. Table 8 summarizes the quantified and non-quantified benefits and costs of excluding these activities from the requirements of the Common Rule.

Table 8. Summary of Estimated Benefits and Costs of Excluding Low-risk Research from the Requirements of the Common Rule (NPRM at §__.101(b)(2))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits	740	605	86.7	86.1

Reduction in number of reviews				
Non-quantified Benefits Clarity in what research activities must be reviewed; ability for IRBs to focus efforts on reviews of higher-risk, more complex, research activities				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

f. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance (NPRM at §__.101(j)

The proposed rule would require consultation among the Common Rule agencies for the purpose of harmonization of guidance, to the extent appropriate, before federal guidance on the Common Rule is issued, unless such consultation is not feasible. The proposal also recognizes that harmonization would not always be possible or desirable given the varied missions of the agencies that oversee the protection of human subjects and differences in statutory authorities. Note that this is a codification of harmonization efforts currently occurring across Common Rule agencies.

This proposal appropriately recognizes the importance of harmonized guidance for the regulated community by creating, as much as possible, consistent interpretations of the regulations.

There is no compliance requirement for the regulated community associated with this provision. It is anticipated that harmonization would create greater uniformity in the regulatory requirements for investigators, institutions, and IRBs, which could reduce confusion and time spent complying with multiple sets of regulations. Costs for achieving harmonization would be borne by the Common Rule agencies.

As this change likely would not impact staffing requirements at Common Rule agencies, no costs are quantified here. It is possible however, that the harmonization requirement could result in it taking longer for Common Rule agency guidance to be approved and issued to the public. Similarly, as it is unclear the extent to which this change would reduce the time IRBs spend on reviewing protocols, benefits are also not quantified. Table 9 summarizes the non-quantified benefits and costs of clarifying and harmonizing regulatory requirements and agency guidance.

Table 9. Summary of Estimated Benefits and Costs of Clarifying and Harmonizing Regulatory Requirements and Agency Guidance (NPRM at §__.101(j))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Increased uniformity in regulatory requirements among Common Rule agencies; increased clarity to the regulated community about how regulations should be interpreted				

COSTS	3 Percent	7 Percent	3 Percent	7 Percent
Quantified Costs None	-	-	-	-
Non-quantified Costs Time for consultation among Common Rule agencies before federal guidance is issued				

g. Expanding the Definition of Human Subject to Include Research involving Non-identified Biospecimens and Creating an Exemption for Secondary Research Using Biospecimens or Identifiable Private Information (NPRM at §§__.102(e), __.101(b)(3)(i), and __.104(f)(2))

The NPRM proposes to expand the definition of human subjects to include research in which an investigator obtains, uses, studies or analyzes a biospecimen. This would apply regardless of the identifiability of the biospecimen. Generally, investigators would not be allowed to remove identifiers from biospecimens without obtaining informed consent or a waiver of consent. Written consent would generally be required for such activities. Thus, this change will significantly expand the amount of research that is subject to the Common Rule. This requirement would not apply to biospecimens and information already collected at the time the final rule is published. Proposed §__.101(b)(3)(i) would exclude research activities involving non-identified biospecimens where no new information about an individual is generated. While activities such as developing new testing assays could be excluded under this provision, it is anticipated that under the NPRM proposals, most research with biospecimens would now fall under the Rule.

At its core, this proposal is intended to promote the ethical principle of respect for persons. In addition to promoting respect for persons in the research enterprise, the proposed regulatory structure for research with biospecimens (whereby consent is sought for almost all research activities involving biospecimens) will encourage investigators to retain identifiers, which can enhance research by preserving the ability to link to important additional information about the subject. Additionally, members of the regulated community have reported situations where, even though not currently required by regulation, investigators were told by an IRB that they needed to obtain study-specific consent for research activities involving non-identified biospecimens. Under the current NPRM proposals, such a situation would not occur because consent—be it broad or study specific—would always be obtained for research involving biospecimens.

While this proposal will promote the ethical principle of respect for persons, it also will significantly increase the volume of studies for which investigators must seek and document informed consent (unless more stringent waiver criteria are met). The RIA estimates that there are 250,000 studies using biospecimens each year that are not currently subject to oversight by either the Common Rule or FDA regulations because they have been stripped of identifiers. Extrapolations from 1999 data[89] suggest that biospecimens are collected from as many as 30 million individuals and are stored each year for both clinical and research purposes. Approximately 9 million individuals' biospecimens (30 percent) are collected for research purposes. As a conservative estimate, approximately 6.3 million individuals' biospecimens (30 percent) could potentially be used in future research studies. Thus, it is possible that

[89] Eiseman, E., Haga, S. (1999). *Handbook of Human Tissue Sources: A National Resource of Human Tissue Samples.* Washington, D.C.: RAND Corporation.

investigators would seek consent to secondary use of biospecimens or a waiver of consent for an additional 15 million individuals annually for secondary use of biospecimens.

In the absence of comprehensive data, to calculate the number of protocols that will now be covered, two approaches are proposed; public comment is requested on these estimates and approaches. Under method one, it is estimated that approximately 50 biospecimens will be used on average per research protocol involving biospecimens. This gives a potential 300,000 new research protocols using non-identified biospecimens. This estimate of 300,000 new research protocols is rounded down to 250,000 new studies because based on ANPRM comments and industry data, it seems reasonable to assume that, as a conservative estimate, the number of new biospecimen studies encapsulated by the proposed rule would equal the total number of new protocols conducted each year (i.e., the number of new biospecimen studies is likely close to the estimate of 246,382 new annual studies).

Under method two, biospecimen repository representatives report that roughly 90 percent of their collections are used in non-identified form in research activities that do not fall under the current Common Rule. Thus, only 10 percent of biospecimen studies are currently covered by the Common Rule, representing a 9:1 ratio of studies involving non-identified biospecimens to studies involving identifiable biospecimens. Of the 246,382 new protocols each year that are non-exempt (Table 3), we assume conservatively that 10-15 percent are using identifiable biospecimens. This equates to between 24,638 and 36,957 new studies each year using identifiable biospecimens. As previously discussed, it is estimated that the number of biospecimen studies that occur on non-identified biospecimens each year is approximately 9

times the number of studies using identifiable biospecimens, or between 221,741 and 332,613 studies each year. Thus, under method two, an estimate of 250,000 new studies on non-identified biospecimens each year is also reasonable.

In order to facilitate research with biospecimens, the NPRM proposes to create separate elements of broad consent (NPRM at §__.116(c), discussed in III.D.2.u below) such that investigators and institutions may seek, and individuals may grant, consent for future unspecified research activities. The NPRM also proposes an exemption that relies on obtaining broad consent for future, unspecified research studies (NPRM at §__.104(f)(2)). In order to be eligible for the exemption proposed in §__.104(f)(2), broad consent must have been sought and obtained using the Secretary's template for broad consent (described in proposed §__.116(d)(3)), and the investigator must not anticipate returning individual research results to subjects. To facilitate secondary research using biospecimens and identifiable private information, the NPRM also proposes an exemption for the storage and maintenance of biospecimens and identifiable private information for future, unspecified, secondary research activities (NPRM at §__.104(f)(1)), which is described in more detail in Section III.D.2.n below).

The exemption proposed at §__.104(f)(2) is specifically for secondary research studies involving biospecimens and identifiable private information that have been or will be acquired for purposes other than the currently proposed research study. If a secondary research study does not meet the requirements of this exemption category, the investigator would need to seek IRB review of the study, and would need to obtain either study-specific consent or a waiver of informed consent under the Common Rule. Note that for biospecimens an IRB would apply the more stringent

waiver criteria at proposed §__.116(e)(2) or (f)(2). For identifiable private information, an IRB would apply the waiver criteria at proposed §__.116(e)(1) or (f)(1), which are almost identical to the waiver criteria in the current Common Rule.

The proposed exemption at §__.104(f)(2), also ensures that in secondary research conducted with biospecimens or identifiable private information, appropriate privacy safeguards are in place (through requiring adherence to the privacy safeguards described in §__.105). Thus, although this provision is an expansion in the nature of research that is exempt, it is accompanied by certain requirements and safeguards.

It is anticipated that a majority of studies that utilize this exemption will be biospecimen studies. The extent to which individuals conducting secondary research studies involving identifiable private information will utilize this exemption is unknown given that there are additional pathways under this proposed rule to facilitate secondary research activities involving identifiable private information is unknown. To that end, the benefits and costs associated with this provision only take into consideration secondary research involving biospecimens. It is further anticipated that these revisions will result in higher value research with biospecimens being conducted with subjects' consent and without the need for full IRB review, or the need to go back to subjects to obtain consent for every secondary research study, as long as certain conditions are met.

Because the estimated 250,000 biospecimen studies each year that will be newly covered under the rule as a result of the proposed modification to the definition of human subject will likely be

low or minimal risk, the RIA assumes that all of these will be eligible for the §__.104(f)(2) exemption (so long as consent—broad or study specific—was sought and obtained). Benefits and costs associated with obtaining and tracking broad consent are discussed below in section III.D.2.u of this RIA. Because the compliance date for the expansion to the definition of human subject will be three years after the date of publication of a final rule, the benefits and costs described below assume a start date of 2019.

As required under §__.104(c), an exemption determination must be made and documented for each of the 250,000 newly covered biospecimen studies. It is anticipated that in 50 percent of these studies (125,000 studies), investigators will spend 30 minutes entering information into the HHS-created decision tool in order for that tool to generate an exemption determination. In the remaining 125,000 studies, it is anticipated that investigators will spend 30 minutes preparing and submitting information about the study to an individual able to make exemption determinations (per §__.104(c)). An individual at the IRB voting member level will spend an estimated 30 minutes per study to make an exemption determination.

In the absence of the proposed exempt category of research at §__.104(f)(2) but taking into consideration the expansion to the definition of human subject, it is estimated that each year, all 250,000 of these studies will undergo convened initial review. In subsequent years, it is estimated estimate that 120,000 protocols would undergo convened initial review, 89,700 would undergo convened continuing review, and 40,300 would undergo expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value costs of $101 million and annualized costs of $11.9 million are estimated using a 3 percent discount rate; present value costs of $77.8 million and annualized costs of $11.1 million are estimated using a 7 percent discount rate. Table 10 summarizes the quantified and non-quantified benefits and costs of amending the definition of human subject.

Table 10. Summary of Expanding the Definition of Human Subject to Include Research involving Non-Identified Biospecimens and Creating an Exemption for Secondary Research Using Biospecimens or Identifiable Private Information (NPRM at §§__.102(e), __.101(b)(3)(i), and __.104(f)(2))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of IRB reviews that would have otherwise occurred as a result of the expansion of the definition of human subject	-	-	-	-
Non-quantified Benefits Ethical benefit of respecting an individual's wishes in how his or her biospecimens are used in future; ensuring				

protection of human subjects in research activities involving non-identifiable biospecimens				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Determining that these studies are exempt in accordance with §__.104(c)	101	77.8	11.9	11.1
Non-quantified Costs Potential reduction in number of biospecimens available for research				

h. Modifying the Assurance Requirements (current Rule at §__.103(b)(1), (b)(3), (d))

The NPRM proposes to modify the requirements of the assurance process in the following ways. First, the NPRM proposes to delete the requirement in the current Common Rule at §__.103(b)(1) of identifying a statement of principles governing all research at an institution. As discussed in section II.H.2 of this preamble, the requirement for institutions to designate a set of ethical principles to which that institution will abide in all research activities is generally not enforced. Further, for international institutions that may receive U.S. government funding for research activities, it creates the impression that these international institutions must modify their internal procedures to comport with the set of principles designated on the FWA for activities conducted at those institutions that receive no U.S. government funding. In order to provide clarity to these international institutions that such measures are not required for activities that receive no Common Rule department or agency support, this provisions has been deleted.

The requirement that a written assurance include a list of IRB members for each IRB designated under the assurance would be replaced by the requirement that the assurance include a statement that for each designated IRB the institution, or when appropriate the IRB, prepares and maintains

a current detailed list of the IRB members with information sufficient to describe each member's chief anticipated contributions to IRB deliberation; and any employment or other relationship between each member and the institution. The regulatory requirement at §__.103(b)(3) that changes in IRB membership be reported to the department or agency head, or to OHRP when the existence of an HHS-approved assurance is accepted, would be deleted, eliminating the requirement. Instead, an institution would be required under proposed §__.108(a)(2) to maintain a current IRB roster, but such a roster would not need to be submitted to OHRP or other agency managing the assurance of compliance process.

The proposed changes to the IRB roster requirement are expected to reduce administrative burden and have the following additional beneficial effects, without having any significant impact on the protection of human subjects:

- Reduction in the administrative burdens on institutions related to the submission of IRB membership lists to OHRP and, in some cases, to the departments and agencies that process their own assurances;
- Reduction in the administrative burdens on OHRP with respect to reviewing and processing new and updated IRB membership lists as part of the IRB registration process, as well as reductions, in some cases, in the administrative burdens on other departments and agencies that receive and review IRB membership lists and changes in IRB membership as part of their own assurance processes;

- In some cases, reduction in the volume of records that need to be created and retained by the departments and agencies regarding the review and processing of IRB membership lists; and
- Simplification of the process for the electronic submission and acceptance of IRB registrations via the OHRP website.

In addition, HHS anticipates modifying the FWA so that institutions would no longer have the option to "check the box" on an assurance and voluntarily extend the funding Common Rule department or agency's regulatory authority to all research conducted at an institution regardless of funding source. For research other than clinical trials, institutions could continue to voluntarily apply the regulations to all research conducted by the institution, but this voluntary extension would no longer be part of the FWA. Members of the regulated community report that whether or not they "check the box" on an assurance form, they tend to voluntarily apply the regulations to all research activities taking place at an institution regardless of funding. Thus, the removal of this option on an assurance form likely would not impact community practice. To that end, no costs have been associated with this provision.

Finally, the current requirement at §__.103(d) that a department or agency head's evaluation of an assurance take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution, would be deleted.

The deletion of this provision would eliminate an administrative process that is no longer meaningful given the purpose and design of the FWA and OHRP's processes for reviewing IRB registrations and reviewing and approving FWAs. This change also harmonizes the Common Rule with FDA's human subjects protection regulations by eliminating the requirement to submit IRB membership lists.

The RIA estimates that administrative staff at each IRB would spend 5 fewer hours complying with the assurance requirements. Based on the estimates presented in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $5.81 million and annualized benefits of $0.68 million are estimated using a 3 percent discount rate; present value benefits of $4.10 million and annualized benefits of $0.58 million are estimated using a 7 percent discount rate. Table 11 summarizes the quantified and non-quantified benefits and costs of the proposed change to the IRB roster requirement.

Table 11. Summary of Estimated Benefits and Costs of Proposed Change to Modifying the Assurance Requirements (current Rule at §__.103(b)(1), (b)(3), (d))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in time for IRB	5.81	4.10	0.68	0.58

administrative staff and OHRP staff to submit, review, and process IRB membership lists				
Non-quantified Benefits Reduction in volume of records created by an institution				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

i. Requirement for Written Procedures and Agreements for Reliance on External IRBs (NPRM at §§__.103(e) and __.115(a)(10))

Language is proposed at §__.103(e) requiring each IRB, institution, or organization that has oversight responsibility for non-exempt research involving human subjects covered by this policy and conducted by another institution to have a written agreement identifying the respective responsibilities of the IRB organization and the engaged institution for meeting the regulatory requirements of this policy. This is already a requirement under the terms of an FWA but this requirement increases the level of detail that has to be included in such agreements, specifically the roles and responsibilities of each party. In addition, a requirement is added at §__.115(a)(10) that institutions or IRBs retain the agreement between the institution and IRB specifying the responsibilities that each entity would undertake to ensure compliance with the requirements of proposed §__.103(e).

The new requirements for agreements between institutions and external IRBs would not apply to research initiated before the effective date of the rule. However, the new requirements would affect existing agreements between institutions and external IRBs in cases where the existing agreements are not study-specific, but rather pertain to all research conducted by the institution or to a category or categories of human subjects research.

Initially, costs would be involved in drafting, revising, and conducting managerial review of agreements to ensure they satisfy these new requirements. Anticipated benefits include enhanced protection of human subjects in research reviewed by nonaffiliated IRBs, and greater reliance on external IRBs as the IRB of record for cooperative research, as stipulated in proposed §__.114.

Table 3 shows that there are 5,164 FWA-holding institutions without an IRB and 2,871 FWA-holding institutions with an IRB. We assume that the 5,164 FWA-holding institutions without an IRB have an average of 1 IRB authorization agreement that would need to be modified as a result of the new requirements for agreements between institutions and external IRBs in 2016. In addition, we assume that the 2,871 FWA-holding institutions with an IRB have an average of 0.20 IRB authorization agreements that would need to be modified in 2016. We estimate that each agreement would require an average of 10 hours of institution legal staff time and 5 hours of IRB administrator time to complete. The dollar value of their time is calculated by multiplying hours by their estimated 2016 wages and adjusting for overhead and benefits.

Present value costs of $11.3 million and annualized costs of $1.32 million are estimated using a 3 percent discount rate; present value costs of $10.8 million and annualized costs of $1.54 million are estimated using a 7 percent discount rate. Table 12 summarizes the quantified and non-quantified benefits and costs of the requirement for written procedures and agreements for reliance on external IRBs (§§__.103(e) and __.115(a)(10) in the NPRM).

Table 12. Summary of Requirement for Written Procedures and Agreements for Reliance on External IRBs (NPRM at §§__.103(e) and __.115(a)(10))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Enhanced human subjects protections in research reviewed by nonaffiliated IRBs and encouragement to institutions to rely on external IRBs when appropriate				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time to modify written agreements between IRBs and institutions	11.3	10.8	1.32	1.54
Non-quantified Costs None				

j. Eliminating the Requirement that the Grant Application Undergo IRB Review and Approval (current Rule at §__.103(f))

The proposed rule would eliminate the requirement in the current Rule at §__.103(f) that grant applications undergo IRB review and approval for the purposes of certification. As described in section II.h.2 of this preamble, the grant application is often outdated by the time the research study is submitted for IRB review and contains detailed information about the costs of a study, personnel, and administrative issues that go beyond the mission of the IRB to protect human subjects. Therefore, experience suggests that review and approval of the grant application is not a productive use of IRB time.

Eliminating the requirement that the grant application undergo IRB review and approval would reduce administrative costs to investigators and IRB voting members. The proposed change likely would not reduce protections for human subjects or impose other costs.

The RIA estimates that there are 324,187 initial reviews of protocols annually, of which 223,689 involve convened review and 100,498 involve expedited review based on the distribution of reviews presented in Table 3. For the purpose of this analysis, it is assumed that each protocol reviewed by an IRB is associated with one grant application or other funding proposal. The RIA estimates that investigators spend an average of 15 minutes compiling their grant applications when they submit a protocol for initial review. Further, it is estimated that IRBs typically use two primary reviewers for convened review and one primary reviewer for expedited review, and that primary reviewers spend an average of 30 minutes reviewing the grant application. Based on the estimates in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $310 million and annualized benefits of $36.3 million are estimated using a 3 percent discount rate, and present value benefits of $219 million and annualized benefits of $31.1 million are estimated using a 7 percent discount rate. Table 13 summarizes the quantified and non-quantified benefits and costs of eliminating the requirement that the grant application undergo IRB review and approval.

Table 13. Summary of Estimated Benefits and Costs of Eliminating the Requirement that the Grant Application Undergo IRB Review and Approval (current Rule at §__.103(f))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Decreased time associated with review	310	219	36.3	31.1
Non-quantified Benefits None				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

k. Tracking and Documenting Exemption Determinations (NPRM at §§__.104(c) and __.115(a)(11))

New in the NPRM is a proposal at §__.104(c) that Federal departments and agencies would develop an exemption determination tool for use by investigators and institutions. Under the proposed rule, unless otherwise required by law, exemption determinations may be made by (1) an individual who is knowledgeable about the exemption categories and who has access to sufficient information to make an informed and reasonable determination, or (2) the investigator who accurately inputs information into the federally created web-based decision tool (NPRM at §___.104(c)). Also new in the NPRM is a requirement at proposed §__.115(a)(11) that an IRB maintain records of exemption determinations. Additionally, proposed §__.104(c) specifies that the use of the exemption determination tool would satisfy the documentation requirement in proposed §__.115(a)(11).

While the documentation requirement for exemption determinations is new, comments from members of the regulated community suggest that most institutions have systems in place already to make and document exemption determinations. Thus, the requirement of proposed §__.115(a)(11) would likely have a negligible impact on institutions. Additionally, it is anticipated that use of the exemption determination tool described in proposed §__.104(c) would likely represent a reduction in burden for institutions and investigators. First, institutions are not responsible for creating the decision tool; the Federal Government is. The costs associated with the development and maintenance of this tool are discussed above in section III.D.2.a of this RIA. Second, except for protocols for which IRB review is required by law and

those for which the exemption tool is unable to issue determinations (and therefore still have to be submitted to an IRB for review), IRB offices would no longer need to devote significant resources to processing and reviewing studies for exemption because the use of the tool by the investigator would suffice. Third, the investigator would no longer need to engage in the time-intensive task of developing and submitting a formal application to an IRB for an exemption determination, which is standard practice at many institutions. Instead, the investigator would be able to answer questions in the to-be-created tool, and then be able to commence work if determination generated by the tool indicates that the proposed research activity meets one of the exemption categories.

The quantifiable benefits and costs associated with the use of the §__.104(c) decision tool are documented in each RIA discussion of exemption categories (sections II.D.2.f, l, m, n of this RIA). Note that while §__104(c) requires that an exemption determination be made before an exempt study may begin, the use of the proposed exemption determination tool is not mandated. Rather, the tool to be created by HHS is an option proposed in order to reduce burden on the investigators and institutions. Additionally, note that at present it is unknown how many studies are exempted under the current Rule each year. Thus, this RIA is only able to provide quantifiable benefits and costs for studies that are estimated to be newly exempted.

Table 14 summarizes the non-quantified benefits and costs of the tracking requirements for exemption determinations and the criteria for those eligible to make exemption decisions in NPRM §___.104(c).

Table 14. Summary of Estimated Benefits and Costs of Tracking and Documenting Exemption Determinations (NPRM at §§__.104(c) and __.115(a)(11))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Reduced administrative burden for IRBs in reviewing exemption determinations, reduced time for investigators to receive an exemption determination.				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

l. Exemption for Research and Demonstration Projects (NPRM at §__.104(d)(2))

The current exemption related to research and demonstration projects (current Rule at §__.101(b)(5)) would be revised to clarify that certain Common Rule agency or department supported activities currently fall within that scope. OHRP also proposes to broaden its interpretation of public benefit and service programs which are being evaluated as part of the research to include public benefit or service programs that an agency does not itself administer through its own employees or agents, but rather funds (i.e., supports) through a grant or contract

program. It has been OHRP's interpretation that the current exemption category 5 only applies to those research and demonstration projects designed to study a "public benefit or service program" that a Common Rule agency or department itself administers, and for which the public benefit or service program exists independent of any research initiative.

The proposed regulatory revision and change in OHRP's interpretation of the exemption is designed to clarify and broaden the scope of the exemption so that more research studies would be exempt. It is believed that these changes would make the exemption easier to apply appropriately and is expected to reduce the number of studies that would be required to undergo IRB review. It is also designed to allow the Federal Government to carry out important evaluations of its public benefit and service programs to ensure that those programs are cost effective and deliver social goods without requiring IRB review and approval. The proposed changes to this exemption would require OHRP to revise its existing guidance document on this exemption accordingly. Costs associated with this revision are accounted for in section III.D.2.a above.

In addition, a requirement has been added that each Federal department or agency conducting or supporting the research and demonstration projects must establish on a publicly accessible federal website or in such other manner as the Secretary of HHS may prescribe, a list of the research and demonstration projects which the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to or upon commencement of the research. This exemption is needed for government entities to carry out activities related to their important public health mission and functions; in

acknowledgement of the fact that more-than-minimal-risk studies could be conducted under this exemption, the posting requirement promotes increased transparency in these activities.

Note that a study's exemption documentation requirement at §__.104(c) is satisfied by a Federal department or agency posting minimal information about the research or demonstration project on a federal, publicly accessible website. Thus, in general, an institutional official would not have to post any information to this website.

It is estimated that approximately 1,000 exempt research and demonstration studies are currently conducted each year.[90] It is further estimated that due to the change in OHRP's interpretation of the research and demonstration project exemption, an additional 3,377 annual reviews of protocols (0.5 percent) would no longer be conducted. Of these 3,377 reviews, 1,118 would have undergone convened initial review, 502 would have undergone expedited initial review, 1,212 would have undergone convened continuing review, and 544 would have undergone expedited continuing review based on the distribution of reviews presented in Table 3. Comment is requested on the accuracy of the estimates of the number of research and demonstration projects conducted each year.

The 4,377 estimated annual studies conducted under this exemption would need to be posted to a federal website as required by §__.104(d)(2)(i). It is anticipated that it would take individuals at the IRB administrative staff level 15 minutes per study to post the study to the website. Note

[90] Estimates based on queries of clinicaltrials.gov and a search of the CMS website. See e.g., http://www.medicaid.gov/medicaid-chip-program-information/by-topics/waivers/waivers_faceted.html, and https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ActiveProjectReports/APR_2011_Edition.html.

that costs related to developing the website to which information about demonstration projects would be posted are calculated in section III.D.2.a of this RIA.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $37.0 million and annualized benefits of $4.34 million are estimated using a 3 percent discount rate, and present value benefits of $30.3 million and annualized benefits of $4.31 million are estimated using a 7 percent discount rate. Present value costs of $0.36 million and annualized costs of $0.04 million are estimated using a 3 percent discount rate; present value costs of $0.30 million and annualized costs of $0.04 million are estimated using a 7 percent discount rate. Table 15 summarizes the quantified and non-quantified benefits and costs of amending an exempt category.

Table 15. Summary of Estimated Benefits and Costs of Amending the Research and Demonstration Project Exemption (NPRM at §__.104(d)(2))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in the number of studies	37.0	30.3	4.34	4.31

requiring IRB review				
Non-quantified Benefits Reduction in time to determine whether the exemption applies to research and demonstration studies; increased transparency to the public in the types of research activities conducted under this exemption				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Communication of the exempt research and demonstration studies	0.36	0.30	0.04	0.04
Non-quantified Costs Possible delays in commencement of exempt research and demonstration studies until posting has occurred; revising federal guidance documents				

m. Expansion of Research Activities Exempt from IRB Review (NPRM at §__.104(d)(3), (e)(1), (e)(2))

Three proposed exemptions in the NPRM would expand the types of activities that could occur without any IRB review (expedited or full-board). A new exemption at proposed §__.104(d)(3) covers research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses (including data entry) or video recording if the subject prospectively agrees to the intervention and data collection and at least one of two criteria is met.

A second exemption at proposed §__.104(e)(1) covers research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or

observation of public behavior (including visual or auditory recording), if the information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects. A third exemption at proposed §__.104(e)(2) would permit the secondary research use of identifiable private information originally collected for non-research purposes, so long as notice was provided to the prospective human subjects about the research activities and the identifiable private information is used only for purposes of the specific research for which the investigator or recipient entity obtained the information.

Because the new exemptions at §__.104(e)(1) and (2) permits investigators to record potentially sensitive information about research subjects in an identifiable form, such activities must comply with the privacy safeguards found at §__.105 in the proposed Rule. Some of this research may be eligible for expedited review under the current rule, and would now be exempt from even that level of IRB review under the proposed rule. This would result in costs savings associated with IRB submission, review, and approval. In addition, most institutions already have information protection systems and policies in place and are likely to already meet the privacy safeguards of proposed §__.105.

It is estimated that 6,754 annual reviews of protocols (0.5 percent) would no longer be conducted as a result of these proposed changes. Of these reviews, 2,236 would have undergone convened initial review, 1,004 would have undergone expedited initial review, 2,424 would have undergone convened continuing review, and 1,088 would have undergone expedited continuing review based on the distribution of reviews presented in Table 3.

As required under §__.104(c), an exemption determination must be made and documented for each of these 6,754 newly exempted studies. It is anticipated that in 50 percent of these studies (3,377 studies), investigators will spend 30 minutes entering information into the HHS-created decision tool in order for that tool to generate an exemption determination. In the remaining 3,377 studies, it is anticipated that investigators will spend 30 minutes preparing and submitting information about the study to an individual able to make exemption determinations (per §__.104(c)). An individual at the IRB voting member level will spend an estimated 30 minutes per study to make an exemption determination.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

The estimated costs associated with new privacy and security standards are presented section III.D.2.o of this RIA. Present value benefits of $70.0 million and annualized benefits of $8.20 million are estimated using a 3 percent discount rate, and present value benefits of $57.2 million and annualized benefits of $8.16 million are estimated using a 7 percent discount rate. Table 16 summarizes the quantified and non-quantified benefits and costs of modifying the exemption categories for research involving adults.

Table 16. Summary of Estimated Benefits and Costs of Creating New Exemption Categories (NPRM at §__.104(d)(3), (e)(1), (e)(2)))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of reviews	70.0	57.2	8.20	8.16
Non-quantified Benefits None				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

n. Exemption for the Storage and Maintenance of Biospecimens and Identifiable Private Information for Future, Unspecified Secondary Research Activities after Consent has been Sought and Obtained (NPRM at §§__.104(f)(1) and __.111(a)(9))

The NPRM proposes a specific exemption for storage and maintenance of biospecimens (regardless of identifiability) and identifiable private information for future, unspecified secondary research activities after consent has been sought and obtained. The idea behind this exemption is that an institution can store and maintain biospecimens and identifiable private information for future research studies without being required to have a specific repository creation protocol developed, reviewed, and approved by an IRB. To be eligible for the exemption, the institution or an investigator must seek broad consent for the future use of biospecimens and information using the Secretary's broad consent template. Biospecimens and

identifiable private information from both the research or non-research contexts may be designated under this exemption for future unspecified research studies. As part of the condition for this proposed exemption, an IRB would be required to do a one-time, limited review of the consent process using the expedited review procedure (as would be required in proposed §__.111(a)(9)). The privacy safeguards outlined in proposed §__.105 would apply to these activities. Note that if moving the biospecimens or information collected for use in future unspecified research studies is envisioned, as part of the limited IRB review described in §__.111(a)(9), an IRB would also need to review the adequacy of the privacy safeguards described in §__.105.

Non-quantified benefits of this provision include clearer instructions to the regulated community about the extent to which creating system for storing and maintaining biospecimens and identifiable private information for future, unspecified secondary research activities is governed by this rule. Additionally, by reducing the IRB burden associated with approving this type of activity, this provision also incentivizes the creation of institution-wide, comprehensive systems for the storage and maintenance of biospecimens and identifiable private information for future, unspecified secondary research activities, which would foster more research while remaining respectful of subject autonomy. Because of the benefits to investigators of being eligible for a new exemption if secondary research activities are conducted using biospecimens or identifiable private information maintained or stored according to §__.104(f)(1), institutions would be further incentivized to implement and develop such a system. Also note that while FDA is unable to harmonize with the Common Rule on many of the exemptions due to specific requirements in

FDA's authorizing statutes, including the §__.104(f)(2) exemption, research that is also subject to the FDA regulations would be eligible for this exemption.

Because of the proposal for the rule to cover all biospecimens regardless of identifiability, it is anticipated that a majority of institutions would elect to develop a system for storing and maintaining biospecimens and identifiable private information for future, unspecified secondary research activities as allowed under the proposed exemption at §__.104(f)(1). This RIA estimates that 6,428 FWA holding institutions (80 percent) would develop such a mechanism for storing and maintaining biospecimens and identifiable private information for future, unspecified secondary research activities. The RIA anticipates that 1,607 FWA institutions (20 percent) would not develop this type of mechanism, either due to the lower volume of research overall conducted at that institution or because the institution conducts mostly social and behavioral research. At each of the 6,428 institutions where a storage and maintenance schema exemptible under NPRM §__.104(f)(1) is developed, it is assumed that an individual at the IRB administrator level would spend two hours at each institution reviewing the consent process through which a subject's broad consent to future research uses of his or her biospecimens or information is sought.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value costs of $1.58 million and annualized benefits of $0.19 million are estimated using a 3 percent discount rate, and present value benefits of $1.48 million and annualized benefits of $0.21 million are estimated using a 7 percent discount rate. Table 17 summarizes the quantified and non-quantified benefits and costs of modifying the exemption categories for research involving adults.

Table 17. Exemption for the Storage and Maintenance of Biospecimens and Identifiable Private Information for Future, Unspecified Secondary Research Activities after Consent has been Sought and Obtained (NPRM at §§__.104(f)(1) and __.111(a)(9))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Fostering research with biospecimens and identifiable private information				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs	1.58	1.48	0.19	0.21

Obtaining limited IRB review of consent process				
Non-quantified Costs None				

o. Privacy Safeguards for Biospecimens and Identifiable Private Information (NPRM at §§__.105 and __.115(c))

Increasing research use of genetic information, information obtained from biospecimens, medical records, and administrative claims data has altered the nature of the risks to those whose information is being used in research. The risks related to these types of research are not physical but rather are informational through, for example, the unauthorized release or use of information about subjects. Currently, IRBs evaluate each study with regard to all levels of risk and are expected to determine whether the privacy of subjects and the confidentiality of their information is protected. Under the current Common Rule, IRBs must review each individual study's protection plan to determine whether it is adequate with respect to the informational risks of that study.

The proposed rule would impose a new requirement that institutions and investigators implement appropriate security safeguards for biospecimens and identifiable private information. The purpose of these safeguards is to assure that access to biospecimens and individually identifiable private information is only authorized in appropriate circumstances and that informational risks are managed by applying appropriate safeguards to information and biospecimens. To ensure that the requisite limitations on use and disclosure are met, an institution or investigator can

obtain adequate assurances through the use of a written agreement with the recipient of the information or biospecimens. In addition, a new provision is proposed at §__.115(c) that requires that the institution or IRB retaining IRB records shall safeguard, if relevant, individually identifiable private information contained in those records in compliance with the privacy safeguards proposed at §__.105.

Under the proposal, the HHS Secretary would develop a set of minimum standards for the protection of information for research outside of the current scope of the HIPAA standards to create an effective and efficient means of implementing appropriate protections for biospecimens and information. This list would be developed in consultation with other Common Rule agencies and would be published in the Federal Register.

Consequently, the IRBs would not be required to review the individual plans for safeguarding information and biospecimens for each research study, so long as investigators would adhere to one or the other set of standards. It is anticipated that once IRBs are familiar with standard institutional- and investigator-imposed protections they would become more comfortable with the fact that they need not review every protocol for security standards. In addition, IRBs would not have to review security provisions on a case-by-case basis, which would result in cost savings in terms of time.

It is expected that most research institutions would already have most of these protections in place, especially those institutions that are subject in whole or part to the HIPAA rules. Other fiduciary, legal, and proprietary responsibilities related to obtaining and storing biospecimens are

likely to encompass the protections proposed for securing biospecimens. Also note that the envisioned security measures that will appear on the Secretary's List would be less stringent than what many institutions have already implemented. It should also be noted that the NPRM proposal would result in uniform baseline standards for security. Costs associated with developing the Secretary's List in accordance with proposed §__.105 are accounted for in section III.D.2.a of this RIA.

It is estimated that 803 of the 8,035 institutions with FWAs (10 percent) would need to update their privacy and security standards to comply with the new requirements. At these institutions, institutional officials and institutional legal staff would each spend an estimated 80 hours in 2016 and 20 hours in subsequent years to update and monitor their privacy and security standards. In addition, the RIA estimates that 43,997 of 439,968 investigators (10 percent) would be required to adopt the updated privacy and security standards. These investigators would each spend an 40 hours in 2016 and 10 hours in subsequent years to comply. Based on the estimates presented in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits. Public comments are requested on these estimates.

Present value costs of $457 million and annualized costs of $53.6 million are estimated using a 3 percent discount rate; present value costs of $347 million and annualized costs of $49.4 million are estimated using a 7 percent discount rate. Table 18 summarizes the quantified and non-quantified benefits and costs to protect information and biospecimens.

Table 18. Summary of Estimated Benefits and Costs of Protection of Information and Biospecimens (NPRM at §§__.105 and __.115(c))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Improved protection of individually identifiable private information and biospecimens				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time for institutions to update and adopt new privacy and security standards	457	347	53.6	49.4
Non-quantified Costs None				

p. Elimination of Continuing Review of Research under Specific Conditions (NPRM at §§__.109(e), (f) and __.115(a)(3), (8))

The NPRM proposes eliminating continuing review for many minimal risk studies, unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects. For studies initially reviewed by a convened IRB, continuing review would not be required, unless specifically mandated by the IRB, after the study reaches the stage where it involves one or both of the following: (1) analyzing data (even if it is identifiable private), or (2)

accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition or disease. If an IRB chooses to conduct continuing review even when these conditions are met, the rationale for doing so must be documented according to a new provision at §__.115(a)(3).

It is also proposed that continuing review of research eligible for expedited review in accordance with §__.110 not be required, although an IRB may determine that continuing review of research eligible for expedited review is necessary. When an IRB requires continuing review of such studies, this too must be documented in compliance with a proposed requirement at §__.115(a)(8).

Requiring continuing review for studies that are minimal risk (and eligible for expedited review at the onset) or that no longer pose greater than minimal risk presents a regulatory burden that does not meaningfully enhance protection of subjects. Further, the requirement takes time from the IRB's review of higher risk studies.

This would result in less time spent by institutions, IRBs, and investigators in terms of time spent preparing for and conducting continuing review. This is a one-time compliance burden in Year 1 for institutions to update their systems to no longer send continuing review reminders to certain investigators. There would be increased recordkeeping requirements, however, for institutions to comply with §__115(a)(3) and (a)(8). Because we estimate that 90 percent of protocols that previously had to undergo continuing view would no longer need to, there is an overall net benefit. However, 10 percent of studies would require a new recordkeeping component. The

benefits in terms of cost savings would begin in year one and extend indefinitely. However, costs would be associated with the requirement that IRBs document cases in which they elect to conduct continuing review when it is not a regulatory requirement.

The RIA estimates that there are 108,873 expedited continuing reviews of protocols annually based on the distribution of reviews presented in Table 3. Of these reviews, the RIA further estimates that 81,546 reviews (75 percent) would not be eliminated by other proposed changes to the Common Rule (such as the modifications proposed at §§__.101(b); __.104(d)(1)-(3), (e)(1), and (f)). It is estimated that 40,773 of these 81,546 reviews (50 percent) would be discontinued and the remaining 40,773 reviews (50 percent) would continue and require documentation of the rationale for doing so. The RIA also estimates that IRB voting members would spend 1 hour per review providing documentation. In addition, administrative staff at each IRB would spend an estimated 10 hours in 2016 updating their communication systems to no longer send continuing review reminders to certain investigators.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $145 million and annualized benefits of $17.0 million are estimated using a 3 percent discount rate, and present value benefits of $119 million and annualized benefits of $16.9 million are estimated using a 7 percent discount rate. Present value costs of

$38.8 million and annualized costs of $4.55 million are estimated using a 3 percent discount rate; present value costs of $31.9 million and annualized costs of $4.54 million are estimated using a 7 percent discount rate. Table 19 summarizes the quantified and non-quantified benefits and costs of the elimination of continuing review of research under specific conditions.

Table 19. Summary of Estimated Benefits and Costs of the Elimination of Continuing Review of Research Under Specific Conditions (NPRM at §§__.109(e), (f) and __.115(a)(3), (8))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of continuing reviews	145	119	17.0	16.9
Non-quantified Benefits None				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time to document rationale for conducting continuing review and update IRB communication systems	38.8	31.9	4.55	4.54
Non-quantified Costs None				

q. Expedited Review Procedures (NPRM at §§__.110 and __.115(a)(9))

The proposed rule would make minor changes regarding expedited review, to change the default position such that expedited review can occur for studies on the HHS Secretary's list unless the reviewer(s) determine(s) that the study involves more than minimal risk. The NPRM also proposes that, in consultation with other Common Rule departments or agencies, the expedited review categories be reviewed every eight years and amended as appropriate, followed by publication in the Federal Register and solicitation of public comment. Finally, there would be a new requirement at proposed §__.115(a)(9) concerning IRB records that IRBs document the rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk (i.e., an override of the presumption that studies on the Secretary's list are minimal risk). Additionally, in order to assist institutions in determining whether an activity is minimal-risk, the NPRM proposes in §__.102(j) that the Secretary of HHS will maintain guidance that includes a list of activities considered to be minimal risk. The costs associated with developing and maintaining this guidance document are accounted for above in III.D.2.a of this RIA.

The proposed changes to the expedited review procedures are expected to reduce the IRB workload by increasing the number of studies that undergo expedited review rather than convened review. The documentation requirement does not produce additional requirements because IRBs must keep records of determinations regardless. This just stipulates that the reason for an override must be described. However, costs would be associated with the requirement that IRBs document cases in which they elect to conduct convened IRB review when it is not a regulatory requirement.

It is estimated that there are 223,689 convened initial reviews and 242,330 convened continuing reviews of protocols annually based on the distribution of reviews presented in Table 3. Of these 223,689 convened initial reviews, it is estimated that 2,237 reviews (1 percent) are eligible for expedited review because they are in a category of research that appears on the HHS Secretary's list. Of these 2,237 reviews, it is estimated that 1,118 reviews (50 percent) would undergo expedited review and the remaining 1,118 reviews (50 percent) would undergo convened review and require documentation of the rationale for doing so.

Of the 242,330 convened continuing reviews, it is estimated that 2,423 reviews (1 percent) are eligible for expedited review because they are in a category of research that would appear on the Secretary's list. Of these 2,423 reviews, the RIA estimates that 1,212 reviews (50 percent) would undergo convened review and would require documentation of the rationale for doing so. Due to the proposed elimination of continuing review of research under specific conditions (§__.109(e) and (f); §__.115(a)(3) and (a)(8)), the remaining 1,212 reviews (50 percent) would not require review. Of these 1,212 reviews, the RIA estimates that 606 reviews (50 percent) would not occur and the remaining 606 reviews (50 percent) would undergo expedited continuing review and require documentation of the rationale for doing so. The RIA estimates that IRB voting members would spend 1 hour per review providing documentation when required. The cost associated with reviewing and amending the list is accounted for in section III.D.2.a of this RIA.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the

estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $16.8 million and annualized benefits of $1.97 million are estimated using a 3 percent discount rate, and present value benefits of $13.7 million and annualized benefits of $1.95 million are estimated using a 7 percent discount rate. Present value costs of $2.71 million and annualized costs of $0.32 million are estimated using a 3 percent discount rate; present value costs of $2.21 million and annualized costs of $0.32 million are estimated using a 7 percent discount rate. Table 20 summarizes the quantified and non-quantified benefits and costs of the elimination of expedited review procedures.

Table 20. Summary of Estimated Benefits and Costs of Amending the Expedited Review Procedures (NPRM at §§__.110 and __.115(a)(9))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of reviews	16.8	13.7	1.97	1.95
Non-quantified Benefits None				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time to document rationale for conducting expedited review	2.71	2.21	0.32	0.32

Non-quantified Costs
None

r. Revised Criteria for IRB Approval of Research (NPRM at §__.111)

Two changes are proposed in the criteria for IRB approval of research. One pertains to the new requirements proposed at §__.105 to protect biospecimens and individually identifiable private information used in research. The regulations at §__.111(a)(7) currently require that in order to approve research covered by this policy, the IRB shall determine that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. This requirement would be modified to recognize that the requirements at §__.105 would apply to all non-exempt research (unless the criteria for exemptions are met). The default position should be that if the provisions at §__.105 are being met, there is no need for additional IRB review of a research study's privacy and confidentiality protections. However, there might be extraordinary cases in which an IRB determines that privacy safeguards above and beyond those called for in §__.105 are necessary. Therefore, it is proposed that IRBs would be responsible for ensuring there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data only if the IRB determines that the protections required in §__.105 are insufficient.

The second proposed change relates to the new exemption at §__.104(f)(2) that includes a criterion at (f)(2)(ii) that the exemptions do not apply if the investigator intends to return individual research results to subjects. Thus, a new provision would be added at §__.111(a)(8) clarifying that IRBs need to review any plan in a research protocol for returning individual

research results to subjects and to determine whether it is appropriate. Although many IRBs probably already review plans for return of results, and many studies do not include this feature, it would not be required that IRBs review all projects to determine if there should be a plan.

The RIA estimates that there are 324,187 initial reviews of protocols annually, of which 223,689 involve convened review and 100,498 involve expedited review based on the distribution of reviews presented in Table 3. The RIA estimates that IRBs typically use two primary reviewers for convened review and one primary reviewer for expedited review, and that primary reviewers spend an average of 15 minutes reviewing the security plans for biospecimens or identifiable private information. Of the 324,187 initial reviews, we estimate that 108,062 reviews (33 percent) would include a plan for returning results to subjects and that primary reviewers would spend an average of 15 minutes reviewing these plans. Based on the estimates in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $126 million and annualized benefits of $14.8 million are estimated using a 3 percent discount rate, and present value benefits of $89.1 million and annualized benefits of $12.7 million are estimated using a 7 percent discount rate. Present value costs of $66.6 thousand and annualized costs of $7.8 thousand using a 3 percent discount rate; present value costs of $62.3 thousand and annualized costs of $8.9 thousand using a 7 percent discount rate. Table 21 summarizes the quantified and non-quantified benefits and costs of the revised criteria for IRB approval of research.

Table 21. Summary of Estimated Benefits and Costs of Revised Criteria for IRB Approval of Research (NPRM at §__.111)

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Decreased time associated with each review	126	89.1	14.8	12.7
Non-quantified Benefits Increased opportunities for research subjects to learn the results of studies in which they participated				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time to review plans for returning results to subjects	0.07	0.06	0.008	0.009
Non-quantified Costs None				

s. Cooperative Research (NPRM at §§__.114, __.103(e), and __.101(a))

The proposed rule would mandate that all domestic sites in a cooperative study rely upon a single IRB for that study, regardless of the source of funding, unless otherwise required by law (e.g., FDA-regulated device studies). Common Rule funding departments or agencies would also have the authority to determine that use of a single reviewing IRB is not appropriate for a particular study (so long as that decision is documented). This policy would apply regardless of whether the study underwent convened IRB review or expedited review. This proposal only affects the

decision about which IRB would be designated as the reviewing IRB for compliance purposes. Related to this is a new provision at §__.103(e) requiring procedures that the institution and IRB would follow for documenting the institution's reliance on the IRB for oversight and the responsibilities of each entity. Also related to this, a new provision at §__.101(a) would give Common Rule departments and agencies the explicit authority to enforce compliance directly against IRBs that are not affiliated with an assured institution. In addition, the proposed rule would be modified to remove the current requirement at §__.103(d) that only with the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another IRB, or make similar arrangements for avoiding duplication of effort.

Currently, the choice to have cooperative research reviewed by a single IRB is voluntary under the Common Rule. In practice, most institutions have been reluctant to replace review by their local IRBs with review by a single IRB in part because of OHRP's current practice of enforcing compliance with the Common Rule through the institutions that were engaged in human subjects research, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB. Review by multiple IRBs for cooperative research can add bureaucratic complexity to the review process and delay initiation of research projects without evidence that multiple reviews provide additional protections to subjects. Thus, the proposed changes at §__.101(a) are included in this NPRM to address this concern in anticipation of greater reliance on external IRBs in cooperative research, and to promote less bureaucratic complexity in the review process in multi-site studies.

Ultimately, these revisions are expected to lower costs associated with multiple reviews for investigators, institutions, and IRBs. There may be some cost shifting as certain IRBs take on the role of reviewing IRB; however, these will be offset by savings at other IRBs no longer required to conduct additional reviews of the same research study. Initially, IRBs and institutions will have to draft and revise their policies regarding their reliance on single IRBs. It is expected that over time standardization in agreements will be achieved, and that reliance on single IRBs will be accepted because of their assured inclusion in oversight, which will result in reduced costs associated with multiple reviews and time savings for investigators who no longer must wait for multiple reviews to occur, with subsequent revisions and amendments. Likely, the hours spent here will replace hours spent reviewing and processing a submission that otherwise would be approved by the institution's IRB.

The OHRP database of registered institutions and IRBs shows that there are 8,035 institutions with an FWA. The RIA estimates that these institutions would develop an average of 10 written joint review agreements with other institutions in 2019 prior to the first year of compliance. The RIA further estimates that each agreement would require an average of 10 hours of institution legal staff time and 5 hours of IRB administrator time to complete. The dollar value of their time is calculated by multiplying hours by their estimated 2016 and 2019 wages and adjusting for overhead and benefits.

It is estimated that there are 202,617 annual reviews of multi-site protocols, and an average of 5 reviews per multi-site protocol, implying that there are 40,523 multi-site protocols reviewed each year. Of these protocols, an estimated 36,471 protocols (90 percent) do not involve medical

devices; as a result, 4 of every 5 reviews would be eliminated. Accordingly, the RIA estimates that 145,884 annual reviews of protocols would no longer be conducted as a result of these proposed changes. Of these reviews, 48,317 would have undergone convened initial review, 21,708 would have undergone expedited initial review, 52,343 would have undergone convened continuing review, and 23,517 would have undergone expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews and based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2019-2025 wages and adjusting for overhead and benefits.

Present value benefits of $1,103 million and annualized benefits of $129 million are estimated using a 3 percent discount rate, and present value benefits of $849 million and annualized benefits of $121 million are estimated using a 7 percent discount rate. Present value costs of $155 million and annualized costs of $18.1 million are estimated using a 3 percent discount rate; present value costs of $138 million and annualized costs of $19.7 million are estimated using a 7 percent discount rate. Table 22 summarizes the quantified and non-quantified benefits and costs of cooperative research.

Table 22. Summary of Estimated Benefits and Costs of Cooperative Research (NPRM at §§__.114, __.103(e), and __.101(a))

	Present Value of 10 Years	**Annualized Value over 10 Years**

	by Discount Rate (Millions of 2013 Dollars)		by Discount Rate (Millions of 2013 Dollars)	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Reduction in number of reviews	1,103	849	129	121
Non-quantified Benefits Standardization of human subjects protections when variation among review IRBs is not warranted				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time requirement to develop model reliance agreement and written joint review agreements	155	138	18.1	19.7
Non-quantified Costs None				

t. Changes in the Elements of Consent, Including Documentation (NPRM at §§__.116(a)(9), (b)(7)-(9), and __.117(b) in the NPRM)

A new element of consent at §__.116(a)(9) applies to identifiable private information collected as part of a research activity. When identifiable private information is collected for research purposes, subjects must be provided with a statement describing the extent to which a subject's information will be made non-identified and used in future activities. An investigator must include in a consent form one of two statements:

- A statement that all identifiable information might be removed from the data and the data that is not identifiable could be used for future research studies or distributed to another

investigator for future research studies without additional informed consent from the subject, if this might be a possibility; or

- A statement that the subject's data collected as part of the research, from which identifiable information is removed, will not be used or distributed for future research studies.

The addition of the requirement to notify subjects of how their non-identified information might be used is viewed as a measure of respect for subjects, by informing them of possible uses of their information. Potential subjects can always decline to participate in the initial research if they are not willing to consent to the statement provided. This measure addresses concerns about people not being fully informed that their non-identified information could be used for research without their consent. These changes are expected to improve informed consent forms and processes, and ideally result in more informed decisions by prospective research subjects about whether to participate in research. The intent is to create greater transparency and improve the informed consent process. This addition would have to meet the documentation requirements at §__.117(b).

While this new provision would require investigators to inform prospective subjects of how their non-identified information originally collected for research purposes might be used in future research studies, it is not expected that this change to have a measurable effect on the administrative costs to the research system. Under the current regulations, a majority of investigators do not restrict the future research use of non-identifiable information. Therefore, it is expected that in implementing this new notification requirement, the vast majority of

investigators would elect option (1). In addition, under the current regulations, investigators may voluntarily restrict the future research use of non-identifiable information, such as in certain research involving vulnerable populations or a rare disease. We do not expect the new notification requirement to result in an increase in the number of investigators who would include option (2) in their consent forms and processes. When investigators choose to restrict the future research use of non-identifiable information under the current Rules, statements about such restricted future use are generally already included in the consent forms and processes. Therefore, for such research, the notification requirement is not expected to result in any change in practice.

Since this notification requirement is not expected to change investigators' secondary use of non-identifiable information originally collected for research purposes, it is anticipated that investigators and institutions already have systems in place to track any restrictions investigators currently choose to implement. As likely is currently the case, it is anticipated that very few investigators would elect to offer the second option listed above because of the challenges of marking and tracking such decisions. Furthermore, since most investigators will likely elect the first option listed above, it would be reasonable for investigators and institutions to assume that the secondary research use of information would be permissible unless marked otherwise. Therefore, it would not be necessary to routinely track information obtained using the first option.

Three additional elements of consent are proposed in §__.116(b)(7)-(9). These three require that a subject be informed of the following, when relevant:

- That the subject's biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- Whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- An option for the subject or the representative to consent, or refuse to consent, to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

These additional elements of consent are proposed to promote the goal of respect for persons and greater transparency in the research enterprise. Additionally, including the information referenced in these provisions in a consent form will help ensure that prospective subjects are given all information necessary for understanding why one might want to participate (or not) in a research study.

The RIA estimates that there are 246,382 new protocols annually using identifiable information. For each protocol, it is estimated that investigators would spend an average of 15 minutes in 2016 updating consent forms to comply with the new requirements found in the NPRM at §__.116(a)(9) or (b)(7)-(9). Based on the estimates presented in Table 3, the dollar value of investigators' time is calculated by multiplying hours by their estimated 2016 wages and adjusting for overhead and benefits.

The RIA assumes that no additional investigators would elect to offer the second option at §__.116(a)(9), and that the investigators who currently offer equivalent options already track the permissible and impermissible uses of information in line with the requirements discussed above. As a result, the RIA estimates that there are no additional costs associated with tracking. Public comment is requested on these assumptions.

Present value costs of $4.55 million and annualized costs of $0.53 million are estimated using a 3 percent discount rate; present value costs of $4.25 million and annualized costs of $0.60 million are estimated using a 7 percent discount rate. Table 23 summarizes the quantified and non-quantified benefits and costs of changes in the basic elements of consent, including documentation.

Table 23. Summary of Estimated Benefits and Costs of Changes in the Elements of Consent, Including Documentation (NPRM at §§__.116(a)(9), (b)(7)-(9) and __.117(b))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Improved informed consent forms and processes				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs	4.55	4.25	0.53	0.60

Time to update consent forms				
Non-quantified Costs None				

u. Obtaining Consent to Secondary Use of Biospecimens and Identifiable Private Information (NPRM at §§__.116(c)(1), (d)(1), (d)(4) and __.117(c)(3))

The NPRM proposes to allow the use of broad consent to secondary research use of biospecimens or identifiable private information for unspecified research purposes. Such broad consent would have specified elements and limitations, and could be collected in both the research and non-research setting.

Given the creation of the exemption for the maintenance and storage of biospecimens and identifiable private information for future, unspecified secondary research activities found in the NPRM at §__.104(f)(1), it is envisioned that institutions creating these research repositories would need to develop tracking systems to monitor which biospecimens or what information may be used in secondary research by investigators. The Secretary of HHS would publish in the Federal Register one or more templates for broad consent (NPRM at §__.116(d)(1)) that would contain all of the required elements of consent for broad, secondary use consent (NPRM at §__.116(c)). If investigators or institutions use the consent template without any changes and seek to use the exemption at §__.104(f)(2), IRB review is not required for these secondary studies, unless IRB review is required by law (e.g., FDA-regulated device studies).

Seeking and obtaining consent to secondary research use of biospecimens and identifiable information is an additional flexibility proposed in the NPRM. However, it is not required. If broad consent has not been sought for the future research use of biospecimens or identifiable private information, then an investigator would need to have his or her project reviewed by an IRB and seek either study-specific consent or a waiver of informed consent under the Common Rule. As discussed in section II.B of this preamble, the NPRM proposes stricter waiver criteria (NPRM at §__.116(e)(2) and (f)(2)) for biospecimens than for identifiable private information; these strict waiver criteria would apply regardless of whether the biospecimens are readily identifiable to the investigator. These waiver criteria would in effect make secondary research using a biospecimen largely impossible in the absence of obtaining subjects' broad consent for future use of their biospecimens. Because investigators would be required to use the Secretary's template for obtaining broad consent in order to be eligible for the new exemptions proposed in §__.104(f), it is expected that minimal time would be spent updating consent forms or drafting wholly new consent forms. OHRP would develop one or more Secretary's templates for obtaining broad consent to secondary use of biospecimens or identifiable private information for subsequent use by investigators and institutions. OHRP staff time associated with developing this resource is accounted for in section III.D.2.a of this RIA.

As discussed earlier in this RIA (section III.D.2.n) it is anticipated that 6,428 FWA holding institutions (80 percent) would store and maintain clinical and non-clinical biospecimens and identifiable private information for unspecified future research studies in the manner prescribed under the new proposed exemption at §__.104(f)(1).

As also discussed previously, extrapolations from 1999 data[91] suggest that biospecimens are collected from as many as 30 million individuals and are stored each year for both clinical and research purposes. Approximately 9 million individuals' biospecimens (30 percent) are collected for research purposes, and thus consent would be sought in the research context for the secondary use of these biospecimens. For these 9 million individuals per year, an investigator would spend an estimated five minutes per person conducting the consent process specific to seeking broad consent, and the subjects would spend an estimated five minutes engaging in the process of having their broad consent for future research uses of their biospecimens or information sought. This estimate of the investigator's time also includes the time for the investigator to log the information into the appropriate database. The RIA further estimates that investigators would spend 10 minutes of time per protocol updating their study-specific consent form to include the language from the Secretary's consent template.

In the clinical setting, approximately 21 million individuals' biospecimens (70 percent of the estimated 30 million individuals' biospecimens collected each year) are collected for clinical purposes. In the first year that the rule is implemented, as many as 21 million broad, secondary use consent forms could be collected from individuals. The RIA anticipates 10 minutes of a subject's time to engage in the consent process. The RIA further anticipates 10 minutes of an institutional employee's time at the IRB Administrative Staff level to seek consent and put the information in the appropriate tracking system.

[91] Eiseman, E., Haga, S. (1999). *Handbook of Human Tissue Sources: A National Resource of Human Tissue Samples.* Washington, D.C.: RAND Corporation.

The NPRM proposes in §__.116(c)(1)(ii)(B) that once an individual gives broad consent to use his or her biospecimens in future, unspecified research studies, that consent may cover any biospecimen collected over the course of a 10 year period. Note that an institution may retain and use the biospecimens collected indefinitely. This provision is merely stating that every 10 years an institution must ask people whether or not they may use newly collected biospecimens in research. Given that an institution must seek broad consent from an individual only once over the course of a 10 year period, it is assumed that after the first year the rule is implemented, the number of individuals from whom an institution seeks broad consent will decrease.

To account for this, the RIA assumes that after the first year that the rule is implemented, a fraction of the clinical subjects from whom secondary use consent is sought in year one would be sought in subsequent years. It is anticipated that in year two, secondary use consent would be sought in the clinical context from 10.5 million subjects (50 percent of the number of individuals involved in the year one estimates). It is anticipated that in year three and after, secondary use consent would be sought in the clinical context from approximately 6.3 million subjects each year (30 percent of the number of individuals involved in the year one estimates). As in year one, the RIA assumes that a prospective subject would spend 10 minutes of time undergoing the consent process and that an institutional employee at the IRB Administrative Staff level would spend 10 minutes of time conducting the consent process with an individual and updating the appropriate tracking system.

Note that assumptions are not made about the extent to which institutions will use the tracked broad consent for the use of identifiable private information. While all institutions that conduct

research with biospecimens will essentially need to create a research repository to continue that type of work under the NPRM proposals, such is not the case with identifiable private information. Identifiable private information is covered under the NPRM as it is under the current Rule. To that end, a research repository containing identifiable private information is not necessary to the research enterprise. Thus, the RIA notes that institutions likely will elect to store identifiable private information in these repositories, but it is unknown the extent to which institutions will elect to do this and the volume of identifiable private information that might be stored. Therefore, estimates are not provided specifically about the potential costs of obtaining broad consent and tracking the consent for future use of identifiable private information.

The costs of the tracking system associated with an institution-wide secondary use research repository are the design, implementation, and operation of the informatics system that would be required to document and keep up with thousands of consent documents per year. In addition, the institution would have to come up with some system to "mark" or otherwise note which biospecimens and pieces of identifiable private information had been consented for use, and which ones had not, to make sure an individual's wishes regarding future use of his or her biospecimens and identifiable private information are carried out. It is estimated that these requirements would impose additional costs to develop or modify existing tracking systems at 80 percent of 8,035 institutions with FWAs. It is estimated that these requirements would require 1.0 database administrator FTEs on average at these institutions. Based on the estimates presented in Table 3, we calculate the dollar value of their time by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits. Public comment is requested on these estimates.

Present value costs of $12,245 million and annualized costs of $1,435 million are estimated using a 3 percent discount rate; present value costs of $8,697 million and annualized costs of $1,238 million are estimated using a 7 percent discount rate. Table 24 summarizes the quantified and non-quantified benefits and costs of obtaining consent to secondary use of biospecimens and identifiable private information.

Table 24. Summary of Estimated Benefits and Costs of Obtaining Consent to Secondary Use of Biospecimens and Identifiable Private Information (NPRM at §§__.116(c)(1), (d)(1), (d)(4) and __.117(c)(3))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Improved informed consent forms and processes, and reduction in time that would have been spent seeking and obtaining consent for secondary research use; retaining identifiers in research; better ensuring of the availability of biospecimens for future research activities				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Time to update consent forms, document, and submit permissible and impermissible secondary uses of data;	12,245	8,697	1,435	1,238

develop and maintain tracking system				
Non-quantified Costs None				

v. Elimination of Requirement to Waive Consent in Certain Subject Recruitment Activities (NPRM at §__.116(g))

The proposed rule would allow an IRB to approve a research proposal in which investigators obtain identifiable private information without individuals' informed consent for the purpose of screening, recruiting, or determining the eligibility of prospective human subjects of research, through oral or written communication or by accessing records, if the research proposal includes appropriate provisions to protect the privacy of those individuals and to maintain the confidentiality of the identifiable private information.

This addresses concerns that the current regulations require an IRB to determine that informed consent can be waived under the current §__.116(d) before investigators may record identifiable private information for the purpose of screening, recruiting, or determining the eligibility of prospective subjects for a research study, provided that the research proposal includes an assurance that the investigator would meet the requirements for protecting the information as described in proposed §__.105. The current requirement is viewed as burdensome and unnecessary to protect subjects, and is inconsistent with FDA's regulations, which do not require a waiver of consent for such recruitment activities.

This should result in some time and cost savings for both investigators and IRBs, but it would likely be small. The savings would come from IRBs no longer needing to consider whether informed consent can be waived for such preparatory-to-research activities. Savings would accrue for investigators who can proceed with such activities in less time.

The RIA estimates that 1,621 annual initial reviews of protocols (0.5 percent) involve a waiver of consent for recruitment activities that would not be required as a result of these proposed changes. Of these reviews, 1,118 would have undergone convened initial review and 502 would have undergone expedited initial review based on the distribution of reviews presented in Table 3. It is estimated that investigators spend an average of 15 minutes requesting a waiver of consent for recruitment activities when they submit a protocol for initial review. It is further estimated that IRBs typically use two primary reviewers for convened review and one primary reviewer for expedited review, and that primary reviewers spend an average of 15 minutes determining whether informed consent can be waived. Based on the estimates in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value benefits of $1.21 million and annualized benefits of $0.14 million are estimated using a 3 percent discount rate, and present value benefits of $0.85 million and annualized benefits of $0.12 million are estimated using a 7 percent discount rate. Table 25 summarizes the quantified and non-quantified benefits and costs of eliminating the requirement to waive consent in certain subject recruitment activities.

Table 25. Summary of Estimated Benefits and Costs of Elimination of Requirement to Waive Consent in Certain Subject Recruitment Activities (NPRM at §__.116(g))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits Decreased time associated with review	1.21	0.85	0.14	0.12
Non-quantified Benefits None				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

w. Requirement for Posting of Consent Forms for Common Rule Agency-Supported Clinical Trials (NPRM at §__.116(h))

A new provision would require that investigators or institutions post a copy of the final version of the consent form for each clinical trial conducted or supported by HHS on a publicly available federal website that would be established as an archive for such consent forms. The name of the clinical trial and information about whom to contact for additional information must be published with the consent form. The consent form must be published on the federal website within 60 days after the trial is closed to recruitment.

It is recognized that certain information contained in an informed consent form is protected from disclosure under the Freedom of Information Act, the Trade Secrets Act, and/or FDA implementing regulations, and, therefore all informed consent forms for FDA-regulated trials covered by this requirement would be subject to redaction before being posted.

It is believed that public posting of consent forms would increase transparency, enhance confidence in the research enterprise, increase accountability, and inform the development of future consent forms, possibly resulting in future savings in time for investigators developing consent forms.

It is expected that the Federal website would enable consent documents to be easily uploaded. Additional costs to the government would involve managing and maintaining the archive.

According to queries of clinicaltrials.gov, there are an estimated 5,270 clinical trials conducted or supported by Common Rule agencies, of which an estimated 575 are regulated by provisions in the Federal Food, Drug, and Cosmetic (FD&C) Act and Trade Secrets Act based on the information presented in Table 3. For the purpose of this analysis, it is assumed that each clinical trial is associated with one consent form that must be submitted to the HHS system by an investigator. The RIA estimates that investigators would spend an average of 15 minutes submitting each consent form. In addition, for the 575 clinical trials regulated by provisions in the FD&C Act and Trade Secrets Act, it is estimated that investigators would spend an average of 30 minutes redacting information before submission.

In addition, submitted consent forms must be reviewed and made accessible to persons with disabilities in compliance with Section 508 Amendment to the Rehabilitation Act of 1973. We estimate that each consent form contains an average of 10 pages and that 508-compliance costs an average of $30 per page. Based on the estimates presented in Table 3, the dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

Present value costs of $14.6 million and annualized costs of $1.71 million are estimated using a 3 percent discount rate; present value costs of $10.4 million and annualized costs of $1.49 million are estimated using a 7 percent discount rate. Table 26 summarizes the quantified and non-quantified benefits and the requirement for posting of consent forms for HHS-supported clinical trials.

Table 26. Summary of Estimated Benefits and Costs of Requirement for Posting of Consent Forms for Common Rule Agency-Supported Clinical Trials (NPRM at §__.116(h))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Increase transparency of HHS-supported clinical trials and inform the development of new consent forms				

COSTS	3 Percent	7 Percent	3 Percent	7 Percent
Quantified Costs Development and management of website, and preparation and submission of consent forms for posting	14.6	10.4	1.71	1.49
Non-quantified Costs None				

x. Alteration in Waiver for Documentation of Informed Consent in Certain Circumstances (NPRM at §__.117(c)(1)(iii))

A new provision would be added allowing a waiver of the requirement to obtain a signed informed consent form if the subjects are members of a distinct cultural group or community for whom signing documents is not the norm. This would be allowed only if the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative method for documenting that informed consent was obtained.

Under the current Rule IRBs may waive the requirement for the investigator to obtain a signed consent form for some or all subjects. The current criteria for such a waiver may not be flexible enough for dealing with a variety of circumstances, such as when federally sponsored research that is conducted in an international setting where, for example, cultural or historical reasons suggest that signing documents may be viewed as offensive and problematic.

This should not involve costs as its intent is to improve the informed consent process by providing more flexibility regarding the documentation of consent, an ethical gain, while reducing administrative requirements for investigators and research subjects in specific circumstances.

Benefits and costs of this new provision are not quantified. Table 27 summarizes the non-quantified benefits and costs of alteration in waiver for documentation of informed consent in certain circumstances.

Table 27. Summary of Estimated Benefits and Costs of Alteration in Waiver for Documentation of Informed Consent in Certain Circumstances (NPRM at §__.117(c)(1)(iii))

	Present Value of 10 Years by Discount Rate (Millions of 2013 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2013 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Improved informed consent process for distinct cultural groups and communities				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs None	-	-	-	-
Non-quantified Costs None				

E. Sensitivity Analysis

The total estimated costs of the proposed changes to the Common Rule are sensitive to assumptions regarding consent to secondary use of biospecimens and information. The RIA estimates that 60 percent of institutions with an assurance would implement a tracking system. Those institutions would require 1.0 FTEs on average to develop and maintain a tracking system. The sensitivity of estimated costs to these baseline assumptions is analyzed by calculating costs under alternative assumptions. That these institutions could instead require 0.75 FTEs or 1.25 FTEs on average to develop and maintain a tracking system is considered. That 50 percent or 70 percent of assurance holding institutions could implement such a tracking system (rather than 60 percent) is also considered. Table 28 reports present value costs using a 3 percent discount rate for these alternative and baseline assumptions.

Table 28. Estimated Present Value Costs Using a 3 Percent Discount Rate (Millions of 2013 Dollars) of Costs of Obtaining Consent to Secondary Use of Biospecimens and Identifiable Private Information Using Baseline and Alternative Assumptions

	Percentage of Institutions that Implement a Tracking System		
FTEs Required at Each Institution	**70 Percent**	**80 Percent**	**90 Percent**
0.75 FTEs	8,700	9,666	10,633
1.00 FTEs	10,956	12,245	13,534
1.25 FTEs	13,212	14,823	16,435

F. Alternative Approaches to the Definition of Human Subject (NPRM at §__.102(e)) and Related Provisions

Two alternative approaches for the treatment of biospecimens under the proposed rule were considered. These alternative proposals centered on concerns about potential identifiability of biospecimens and data derived from biospecimens.

Alternative Proposal A: Expand the Definition of "Human Subject" to Include Whole Genome Sequencing (WGS)

Under Alternative Proposal A, the regulations at proposed §__.102(e) would be amended to expand the definition of human subjects to include more specifically whole genome sequencing data, or any part of the data generated as a consequence of whole genome sequencing, regardless of the individual identifiability of specimens used to generate such data. Investigators would not be allowed to remove identifiers from specimens or data to conduct whole genome sequencing without obtaining informed consent or a waiver of consent, because obtaining whole genome sequencing data about an individual would in and of itself cause the individual to meet the definition of a human subject. Written consent would generally be required for such activities. This requirement would not apply to specimens and information already collected at the time the final rule is published.

Recent developments have made it possible to use whole genome sequencing information to re-identify non-identified data. Thus, even if such information is not "individually identifiable" (per the current Rule's standard of identifiability) it is appropriate to expand the definition of human subjects research in this way to afford individuals who are the subjects of such research the same

protections as those given to the subjects of research using identifiable information or specimens. Therefore, it is anticipated that this change would increase protections for subjects of whole genome sequencing research. It would also increase the volume of studies for which investigators must seek and document informed consent, unless more stringent waiver criteria were met, and institutions will have to track the consent status of specimens and data. In addition, IRBs would have to review these studies unless the research meets the new proposed exemption in proposed §__.104(f)(2).

It is estimated that there are 300 studies using whole genome sequencing data that are not subject to oversight by either the Common Rule or FDA regulations. This RIA estimates that under this alternative, 90 percent of these studies (270) would be eligible for the exemption proposed in §__.104(f)(2). For the remaining 30 studies, it is anticipated that these would not be eligible for the exemption, and would require full IRB review. As required under §__.104(c), an exemption determination would be made and documented for each of the 270 exemptible whole genome sequencing studies. It is anticipated that in 50 percent of these studies (135 studies), investigators will spend 30 minutes entering information into the HHS-created decision tool in order for that tool to generate an exemption determination. In the remaining 135 studies, it is anticipated that investigators will spend 30 minutes preparing and submitting information about the study to an individual able to make exemption determinations (per §__.104(c)). An individual at the IRB voting member level will spend an estimated 30 minutes per study to make an exemption determination.

In the absence of the proposed exempt category at §__.104(f)(2), we estimate that in 2016 all 300 of these studies would undergo convened initial review. In subsequent years, an estimated 144 protocols would undergo convened initial review, 108 would undergo convened continuing review, and 48 would undergo expedited continuing review, based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

For Alternative Proposal A, present value costs of $0.57 million and annualized costs of $0.07 million are estimated using a 3 percent discount rate; and present value costs of $0.47 million and annualized costs of $0.07 million are estimated using a 7 percent discount rate. Table 29 summarizes the quantified and non-quantified benefits and costs of amending the definition of human subject.

Table 29. Summary of Estimated Benefits and Costs of the Alternative Proposal A for Modifying the Definition of Human Subject (NPRM at §__.102(e))

	Present Value of 10 Years by Discount Rate (Millions of 2014 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2014 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**

Quantified Benefits None	-	-	-	-
Non-quantified Benefits Ensuring human subjects are protected in whole genome sequencing research not currently subject to oversight				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Increase in number of reviews	0.57	0.47	0.07	0.07
Non-quantified Costs Time to obtain consent for activities involving whole genome sequencing				

Alternative Proposal B: Classifying Certain Biospecimens Used in Certain Technologies as Meeting the Criteria for "human subject"

Under Alternative Proposal B, the regulations at proposed §__.102(e) would be expanded to include biospecimens used in a technology capable of producing biologically unique information about a subject as well as the biologically unique information derived from a biospecimen. Only those technologies specifically listed on a newly created Secretary's List would be considered to have met this definition. For example, if whole genome sequencing was a technology included on the Secretary's List, then activities where a biospecimen (regardless of the investigator's ability to readily identify the person from whom the biospecimen was collected) was used in whole genome sequencing research would be subject to the rules. Additionally, activities involving the information generated from a biospecimen used in a technology that appeared on this Secretary's List (regardless of the investigator's ability to readily identify a subject) would

also fall under these regulations. Information derived from a technology appearing on the Secretary's List described above would be referred to as "bio-unique" information.

This expansion would modestly increase the studies encompassed under the rule. This estimate is based on what is known about whole genomic research technologies that results in genome sequencing data (including DNA and RNA sequence data) that is unique to a single individual. It is estimated that there are 898 genomic research studies not currently subject to oversight that result in genome sequencing data unique to a single individual.

One of the primary objectives of the NPRM has been to make the strength of protections commensurate with the level of risks of the research, and by doing so reduce unnecessary administrative burdens on research. That objective has been viewed as being particularly relevant to research involving only secondary use of biospecimens and data, which is relatively low-risk if appropriate protections of privacy and confidentiality are in place. Alternative Proposal B targets activities involving biospecimens where concerns about information risks indicate that additional regulatory oversight for these studies is appropriate.

When the proposed exemption category at §__.104(f)(2) is considered, this RIA estimates that under Alternative Proposal B, 808 studies (90 percent) would be eligible for exemption. For the remaining 89 studies, it is anticipated that these would not satisfy the §__.104(f)(2) requirements and would require full IRB review.

As required under §__.104(c), an exemption determination would be made and documented for each of the 808 exemptible genomic research studies described above. It is anticipated that in 50 percent of these studies (404 studies), investigators will spend 30 minutes entering information into the HHS-created decision tool in order for that tool to generate an exemption determination. In the remaining 404 studies, it is anticipated that investigators will spend 30 minutes preparing and submitting information about the study to an individual able to make exemption determinations (per §__.104(c)). An individual at the IRB voting member level will spend an estimated 30 minutes per study to make an exemption determination.

In the absence of the proposed exempt category of research at §__.104(f)(1), the RIA estimates that as a result of the proposed expansion to the definition of human subject, all 898 of these studies would undergo convened initial review. In subsequent years, an estimated 431 protocols will undergo convened initial review, 322 will undergo convened continuing review, and 145 will undergo expedited continuing review based on the distribution of reviews presented in Table 3.

The estimated costs to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews are based on the estimates presented in Table 3. The dollar value of their time is calculated by multiplying hours by their estimated 2016-2025 wages and adjusting for overhead and benefits.

For Alternative B, present value costs of $1.69 million and annualized costs of $0.20 million are estimated using a 3 percent discount rate; present value costs of $1.39 million and annualized

costs of $0.20 million are estimated using a 7 percent discount rate. Table 30 summarizes the quantified and non-quantified benefits and costs of amending the definition of human subject.

Table 30. Summary of Estimated Benefits and Costs of the Alternative Proposal B for Modifying the Definition of Human Subject (NPRM at §__.102(e))

	Present Value of 10 Years by Discount Rate (Millions of 2014 Dollars)		**Annualized Value over 10 Years by Discount Rate (Millions of 2014 Dollars)**	
BENEFITS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Benefits None	-	-	-	-
Non-quantified Benefits Ensuring that informational risks are minimized in research activities involving technologies capable of producing bio-unique information				
COSTS	**3 Percent**	**7 Percent**	**3 Percent**	**7 Percent**
Quantified Costs Increase in number of reviews	1.69	1.39	0.20	0.20
Non-quantified Costs Time to obtain consent for activities involving the generation or use of bio-unique information				

G. Regulatory Flexibility Analysis

As discussed above, the RFA requires agencies that issue a regulation to analyze options for regulatory relief of small entities if a rule has a significant impact on a substantial number of

small entities. HHS considers a rule to have a significant economic impact on a substantial number of small entities if at least 5 percent of small entities experience an impact of more than 3 percent of revenue.

We calculate the costs of the proposed changes to the Common Rule to institutions with an FWA over 2016-2025 and then subtract the cost savings to these institutions over the same period. The estimated average annualized net cost to institutions with an FWA is $153,671 using a 3 percent discount rate. The U.S. Small Business Administration establishes size standards that define a small entity. According to these standards, colleges, universities, and professional schools with revenues below $27.5 million and hospitals with revenues below $38.5 million are considered small entities. It is not anticipated that a majority of institutions with an FWA are in one of these categories.

IV. Environmental Impact

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

V. Paperwork Reduction Act

This proposed rule contains collections of information that are subject to review and approval by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA), as

amended (44 U.S.C. 3501-3520). A description of these provisions is given in this document with an estimate of the annual reporting and recordkeeping burden.

We invite comments on these topics: (1) The accuracy of the estimate of burden of the proposed collection of information; (2) ways to enhance the quality, utility, and clarity of the information to be collected; and, (3) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information and technology.

Title: Federal Policy for the Protection of Human Subjects.

Description: In this document is a discussion of the regulatory provisions we believe are subject to the PRA and the probable information collection burden associated with these provisions. In general, the following actions trigger the PRA: (i) Reporting; (ii) Disclosure; (iii) Recordkeeping.

Description of Respondents: The reporting and recordkeeping requirements in this document are imposed on Institutions, Institutional Review Boards, and Investigators involved in human subjects research conducted or supported or otherwise subject to regulation by any Federal department or agency that takes administrative action that makes the policy applicable to such research.

§__ .101. To what does this policy apply (OMB Control No 0990-0260)

Section __.101 is being amended to place unaffiliated Institutional Review Boards (IRBs) within the realm of entities to which the policy applies as described in §__.101(a) . This new provision gives Common Rule departments and agencies explicit authority to enforce compliance directly against IRBs that are not affiliated with an assured institution. This change should encourage institutions to more willingly rely on qualified unaffiliated IRBs for cooperative research, as is required under the proposed changes at §__.114. Burden estimates are included below in §__.114 summary.

Section __.101 is also being amended to extend the regulations to cover clinical trials conducted at an institution in the United States that receives federal support from a Common Rule department or agency for non-exempt human subjects research, regardless of the funding source of the trial as described in §__101(a)(2)**.** Extension of the regulations would not apply to clinical trials already regulated by FDA. We estimate that there are 1,399 clinical trials currently not subject to oversight by either the Common Rule or FDA regulations. We estimate that in 2016 all 1,399 of these clinical trials will undergo convened initial review. In subsequent years, we estimate that 672 protocols will undergo convened initial review, 502 will undergo convened continuing review, and 225 will undergo expedited continuing review. We estimate the burden to institution officials, IRB administrators, IRB administrative staff, IRB chairs, IRB voting members, and investigators of conducting these reviews (24 hours per protocol) based on the estimates presented in Table 3 of section III of the preamble.

§__.103. Assuring compliance with this policy -- research conducted or supported by any Federal Department or Agency (OMB Control No. 0990-0260)

Section __.103 is being amended, at §__.103(e), to require that for non-exempt research involving human subjects covered by this policy that takes place at an institution in which IRB oversight is conducted by an unaffiliated IRB that is not operated by the institution, the institution and the organization operating the IRB shall establish and follow procedures for documenting the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between the institution and the IRB, or by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution). Burden estimates are included below in §__.114.

§__.104 Exempt research (OMB Control No. 0990-0260)

Section __.104 is being proposed, as described in §__.104(c), to require federal departments and agencies to develop a decision tool to assist in exemption determinations. Under the proposed rule, unless otherwise required by law, exemption determinations may be made by an individual who is knowledgeable about the exemption categories and who has access to sufficient information to make an informed and reasonable determination, or by the investigator or another individual at the institution who enters accurate information about the proposed research into the decision tool, which would provide a determination as to whether the study is exempt. If the tool

is used, further assessment or evaluation of the exemption determination is not required. Burden estimates are included below in §__.115(a)(11).

Section __.104 is being proposed, as described in §__.104(d)(2), to require each federal department or agency conducting or supporting the research or demonstration projects exempted under §__.104(d), to establish on a publicly accessible federal website or in such other manner as the department or agency head may prescribe, a list of the research and demonstration projects that the federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to or upon commencement of the research. We estimate that 4,377 exempt research and demonstration studies will be posted to the website annually, and that the information will be submitted to the website by individuals at the IRB administrative staff level, an estimate of 1.82 person- hours per protocol (7966.14 burden hours).

§__.105 Protection of Biospecimens and Identifiable Private Information, (OMB Control No. 0990-0260)

Section __.105 is being proposed, as detailed in §__.105(a), to require institutions and investigators conducting research subject to the Common Rule, or that is exempt under §§__.104(e) or (f) to implement and maintain reasonable and appropriate safeguards to protect biospecimens, or identifiable private information they collect, store or use for research. The Secretary of HHS will establish and publish a list of specific measures that the institution or investigator may implement that will be deemed to satisfy the requirement for reasonable and

appropriate safeguards. The list will be evaluated as needed, but at least every 8 years, and amended, as appropriate, after consultation with other federal departments and agencies. Institutions and investigators may choose either to apply the safeguards identified by the Secretary as necessary to protect the security or integrity of and limit disclosure of biospecimens and electronic and non-electronic identifiable private information or to apply safeguards that meet the standards in 45 CFR 164.308, 164.310, 164.312, and 45 CFR 164.530(c). For federal departments and agencies that conduct research activities that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3601 et seq., if all of the information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and the research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq., these research activities automatically will be considered in compliance with the Secretary's reasonable and appropriate safeguards standards, unless or until any additional safeguards are identified by the Secretary of HHS.

We estimate that 803 of the 8,035 institutions with FWAs (10 percent) will be required to update their privacy and security standards to comply with the new requirements. At these institutions, we estimate that institutional officials and institutional legal staff will each spend 80 hours in 2016 and 20 hours in subsequent years to update and monitor their privacy and security standards. In addition, we estimate that 43,997 of 439,968 investigators (10 percent) will be required to adopt the updated privacy and security standards. We estimate that these investigators will each spend 40 hours in 2016 and 10 hours in subsequent years to do so.

§__.111 Criteria for IRB approval of research, (OMB Control No. 0990-0260)

Section __.111 is being amended at §__.111(a)(8) to add a new requirement that if the investigator proposes a research plan for returning relevant results to subjects, then the IRB must determine that the plan is appropriate. We estimate that there are 324,187 initial reviews of protocols annually. Of the 324,187 initial reviews, we estimate that 108,062 reviews (33 percent) will include a plan for returning results to subjects and that primary reviewers will spend an average of 15 minutes reviewing these plans.

§__.114 Cooperative research (OMB Control No 0990-0260)

Section __.114 is being amended, as described in §__.114(b)(1) to require any institution located in the United States (U.S.) that is engaged in cooperative research to rely upon approval by a single IRB for that portion of the research conducted in the U.S. As described in §__.114(b)(2), cooperative research for which more than single IRB review is required by law (e.g., FDA-regulated device studies); or research for which the federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular study need not comply with this requirement. The OHRP database of registered institutions and IRBs shows that there are 8,035 institutions with an FWA. We estimate that these institutions will develop an average of 10 written joint review agreements with other institutions in 2018 prior to the first year of compliance. We estimate that each

agreement will require an average of 10 hours of institution legal staff time and 5 hours of IRB administrator time to complete.

§__.115 IRB records (OMB Control No 0990-0260)

Section __.115 is being amended, in §__.115(a)(8), to require the rationale for requiring continuing review for research that otherwise would not require continuing review as described in §__.109(f)(1).

We estimate that there are 108,873 expedited continuing reviews of protocols annually based on the distribution of reviews presented in Table 3 of the Regulatory Impact Analyses section of the preamble. Of these reviews, we estimate that 81,546 reviews (75 percent) will not be eliminated by other proposed changes to the Common Rule at §§__.101(b), __.104(d)(1)-(3), __.104(e)(1). We estimate that 40,773 of these 81,546 reviews (50 percent) will be discontinued and the remaining 40,773 reviews (50 percent) will continue and require documentation of the rationale for doing so. We estimate that IRB voting members will spend 1 hour per review providing documentation. In addition, we estimate that administrative staff at each IRB (total of 3,499 IRBs) will spend 10 hours in 2016 updating their communication systems to no longer send continuing review reminders to certain investigators.

Section __.115 is being amended at §__.115(a)(9) to require that the rationale for an expedited reviewer's determination that research appearing on the expedited list described in

§__.111(b)(1)(i) is more than minimal risk (i.e., an override of the presumption that studies on the Secretary's list are minimal risk).

We estimate that there are 223,689 convened initial reviews and 242,330 convened continuing reviews of protocols annually based on the distribution of reviews presented in Table 3 of the Regulatory Impact Analyses section of the preamble. Of these 223,689 convened initial reviews, we estimate that 2,237 reviews (1 percent) are eligible for expedited review because they are in a category of research that appears on the Secretary's list. Of these 2,237 reviews, we estimate that 1,118 reviews (50 percent) will undergo expedited review and the remaining 1,118 reviews (50 percent) will undergo convened review and require documentation of the rationale for doing so.

Of the 242,330 convened continuing reviews, we estimate that 2,423 reviews (1 percent) are eligible for expedited review because they are in a category of research that appears on the HHS Secretary's list. Of these 2,423 reviews, we estimate that 1,212 reviews (50 percent) will undergo convened review and will require documentation of the rationale for doing so. Due to the proposed elimination of continuing review of research under specific conditions (§§__.109(f); __.115(a)(3), (8)), the remaining 1,212 reviews (50 percent) will not require review. Of these 1,212 reviews, we estimate that 606 reviews (50 percent) will not occur and the remaining 606 reviews (50 percent) will undergo expedited continuing review and require documentation of the rationale for doing so. We estimate that IRB voting members will spend 1 hour per review providing documentation when required.

Section__.115 is being amended, at §__.115(a)(10) to require the written agreement between an institution and an external IRB specifying the responsibilities that each entity will undertake to ensure compliance with the requirements described in §__.103(e).

Table 3 of section III of the preamble shows that there are 5,164 FWA-holding institutions without an IRB and 2,871 FWA-holding institutions with an IRB. We assume that the 5,164 FWA-holding institutions without an IRB have an average of 1 IRB authorization agreement that would need to be modified as a result of the new requirements for agreements between institutions and external IRBs in 2016. In addition, we assume that the 2,871 FWA-holding institutions with an IRB have an average of 0.20 IRB authorization agreements that would need to be modified in 2016. We estimate that each agreement will require an average of 10 hours of institution legal staff time and 5 hours of IRB administrator time to complete.

Section __.115, is being amended, in §__.115(a) (11), to require records relating to exemption determinations as described in §__.104(c). As part of this new requirement, OHRP will create an interactive exemption determination tool. We estimate that 6,754 annual reviews of protocols would no longer be conducted as a result of proposed changes under §__.104. As required under §__.104(c), an exemption determination must be made and documented for each of these 6,754 newly exempted studies. It is anticipated that in 50 percent of these studies (3,377 studies), investigators will spend 30 minutes entering information into the HHS-created decision tool in order for that tool to generate an exemption determination. In the remaining 3,377 studies, it is anticipated that investigators will spend 30 minutes preparing and submitting information about the study to an individual able to make exemption determinations (per §__.104(c)). An

individual at the IRB voting member level will spend an estimated 30 minutes per study to make an exemption determination.

§§__.116 and __.117 General requirements for informed consent (OMB Control No 0990-0260)

Section __.116 is being amended, as described in §__.116(a)(9), to add a new basic element of consent that would apply to any research collection of identifiable private information. One of the following statements about such research collection much be provided to subjects: (i) a statement that identifiers might be removed from the data and the data that is not identifiable could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the representative, if this might be a possibility; or, (ii) a statement that the subject's data collected as part of the research, from which identifiers are removed, will not be used or distributed for future research studies. We estimate that there are 246,382 new protocols annually using individually identifiable information. For each protocol, we estimate that investigators will spend an average of 15 minutes in 2016 updating consent forms to comply with the new requirements.

Section __.116 is being amended, as described in §__.116(c) to allow broad consent to cover the storage, maintenance, and secondary research use of biospecimens and identifiable private information. Broad consent would be permissible for the storage or maintenance for secondary research of such information and biospecimens that were originally collected for either research studies other than the proposed research or non-research purposes. The broad consent document would also meet the consent requirement for the use of such stored biospecimens and

information for individual research studies.

We anticipate 6,428 FWA holding institutions (80 percent) will develop an institution-wide research repository of biospecimens and identifiable private information available for future research in the manner prescribed under the new proposed exemption at §__.104(f)(1). We estimate that 80 percent of institutions with an FWA (6,428 institutions) will implement a tracking system. Those institutions will require 1.0 FTEs on average to develop and maintain a tracking system.

It is anticipated that many investigators will choose to seek such consent in order to save time and burden by avoiding the need to (1) seek and obtain consent to every specific future research use, (2) seek full IRB review for research that meets one of the exempt research categories, or (3) seek IRB review for a waiver of consent.

Section__.116 is being amended, as described in §__.116(h), to require that a copy of the final version of the consent form for each clinical trial conducted or supported by a Federal department or agency component conducting the trial on a publicly available federal web site that will be established as a repository for such consent forms. The informed consent form must be posted in such form and manner as the department or agency head may prescribe, which will include at a minimum posting, in addition to the informed consent form, the name of the clinical trial and information about whom to contact for additional details about the clinical trial. The consent form must be published on the federal website within 60 days after the trial is closed to recruitment.

We estimate that Common Rule departments and agencies supports 5,270 new clinical trials annually, of which 575 are regulated by provisions in the FD&C Act and Trade Secrets Act based on the information presented in Table 3 of the Regulatory Impact Analyses section of the preamble. For the purpose of this analysis, we assume that each clinical trial is associated with one consent form that must be submitted by an investigator. We estimate that investigators will spend an average of 15 minutes submitting each consent form. In addition, for the 575 clinical trials regulated by provisions in the FD&C Act and Trade Secrets Act, we estimate that investigators will spend an average of 30 minutes redacting information before submission.

Table 30 – Estimated Annual Reporting Burden

Sec. Description	Description of burden	Num. of Respondents	Num. of responses per respondent	Total annual responses	Avg. Hrs per response	Total Hrs
101(a)(2)--Expansion of rule to cover clinical trials not otherwise regulated by the FDA	Initial review	1,399.00	1.00	1,399.00	24.00	33,576.00
104(d)(2)(i)--Posting requirement for research and demonstration projects	Posting minimal information about study to federal website	4,377.00	1.00	4,377.00	1.82	7,966.14
105—Protection of Biospecimens and Identifiable Private information	IOs and legal staff to develop policies and procedures to implement standards	803.00	1.00	803.00	80.00	64,240.00
105--Biospecimen and information safe guards	time for investigators to comply with new requirements	43,997.00	1.00	43,997.00	40.00	1,759,880.00

Sec. Description	Description of burden	Num. of Respondents	Num. of responses per respondent	Total annual responses	Avg. Hrs per response	Total Hrs
111(a)(8)--IRB review of plans to return research result	IRB reviewer time to review plans to return research results	108,062.00	1.00	108,062.00	0.25	27,015.50
114--New requirement for one IRB of record for multi-site studies	Time to create agreements for all institutions involved in a study will rely on one IRB of record	8,035.00	1.00	8,035.00	15.00	120,525.00
115(a)(8)--Documenting IRB rationale for requiring continuing IRB review for research that would otherwise not require it	Create documentation	40,773.00	1.00	40,773.00	1.00	40,773.00
115(a)(8)--Documenting IRB rationale for requiring continuing IRB review for research that would otherwise not require it	Update systems	3,499.00	1.00	3,499.00	10.00	34,990.00

Sec. Description	Description of burden	Num. of Respondents	Num. of responses per respondent	Total annual responses	Avg. Hrs per response	Total Hrs
115(a)(9)--Documenting IRB rationale for determining that research on the expedited review list is more than minimal risk	Initial review	1,118.00	1.00	1,118.00	1.00	1,118.00
115(a)(9)--Documenting IRB rationale for determining that research on the expedited review list is more than minimal risk	Continuing review	606.00	1.00	606.00	1.00	606.00
115(a)(10)--Written agreement btwn institutions and unaffiliated IRBs documenting responsibilities	Institutions with no IRB agreement modifications	5,164.00	1.00	5,164.00	15.00	77,460.00
115(a)(10)--Written agreement btwn institutions and unaffiliated IRBs documenting responsibilities	Institutions with IRB agreement modifications	2,871.00	0.20	574.20	15.00	8,613.00

Sec. Description	Description of burden	Num. of Respondents	Num. of responses per respondent	Total annual responses	Avg. Hrs per response	Total Hrs
115(a)(11)--Records related to exemption determinations	IRB offices processing documentation	40,773.00	1.00	40,773.00	11.00	448,503.00
116(a)(9) & 117(b)(2)--New required element of informed consent telling subjects how their non-identifiable data or specimens might be used	Updating IC forms	246,382.00	1.00	246,382.00	0.25	61,595.50
116(c) & 117(c)(3)--Obtaining and documenting broad secondary use consent	Obtain consent research setting	9,000,000.00	1.00	9,000,000.00	0.25	2,250,000.00
116(c) & 117(c)(3)--Obtaining and documenting broad secondary use consent	Obtain consent non-research setting	21,000,000.00	1.00	21,000,000.00	0.17	3,570,000.00
116(c) & 117(c)(3)--Obtaining and documenting broad secondary use consent	Modify tracking system	21,000,000.00	1.00	21,000,000.00	0.17	3,570,000.00
116(h)--Requirement to post consent forms for clinical trials	Posting consent forms for new clinical trials	5,270.00	1.00	5,270.00	0.25	1,317.50

Sec. Description	Description of burden	Num. of Respondents	Num. of responses per respondent	Total annual responses	Avg. Hrs per response	Total Hrs
116(h)--Requirement to post consent forms for clinical trials	Posting consent forms for clinical trials already regulated by FD&C and trade secrets act regulations	575.00	1.00	575.00	0.50	287.50
TOTAL						**12,155,926.14**

The total estimated burden imposed by these information collection requirements is 12,155,926 burden hours.

It should be noted that the burden estimates for the Common Rule include those approved information requirements in: (1) OMB No. 0990-0260, Protection of Human Subjects: Compliance with Federal Policy/IRB Recordkeeping/Informed Consent/Consent Documentation, approved through May 31, 2018; (2) OMB No. 0990-0263, Assurance Identification/IRB Certification/Declarations of Exemption Form (Common Rule), approved through March 31, 2018; (3) OMB No. 0990-0278, Federalwide Assurance (FWA) for the Protection of Human Subjects, approved through August 31, 2017; and, (4) OMB No. 0990-0279, HHS, Registration of an Institutional Review Board ((IRB), approved through August 31, 2015. As such, they will

be amended and submitted to OMB as revisions to currently approved collections once the rule is finalized and the collections are due for renewal.

To ensure that comments on these new information collection requirements are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn:[OS Desk Officer, FAX: 202-395-6974, or emailed to oira_submission@omb.gov. All comments should be identified with the title "Federal Policy for the Protection of Human Subjects."

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the information collection provisions of this proposed rule will be submitted to OMB for review. These requirements will not be effective until OMB approves them.

VI. Summary of Comments Received on the 2011 Common Rule ANPRM

A. Initial Step Toward Modernization of the Common Rule: The Advance Notice of Proposed Rulemaking (ANPRM)

In considering changes in the Common Rule, the ANPRM requested comment on possible changes to seven aspects of the current regulatory framework.

1. Ensuring Risk-Based Protections
2. Streamlining IRB Review of Cooperative Studies

3. Improving Informed Consent
4. Strengthening Data Protections to Minimize Information Risks
5. Data Collection to Enhance System Oversight
6. Extension of Federal Regulations
7. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Public comments on the ANPRM initially were requested by September 26, 2011; however, in response to public requests for an extension, the comment period was extended until October 26, 2011. A total of 1,051 comments were received, with many commenters responding to all 74 questions posed. Investigators comprised the largest group of commenters. Comments were also received from: trade and professional associations; medical and social/ behavioral research organizations; disease and patient advocacy groups; IRB members and staff; individual, private companies and the organizations representing them; and patients and research subjects. A large number of comments were lengthy and detailed, reflecting thoughtful consideration of the issues discussed. Many responses reflected the input of large research and health care organizations, including public university systems, research universities, academic medical centers, and medical schools, as well as networked health care providers. The greatest number of comments focused on the section addressing risk-based protections.

In addition to reviewing the public responses to the ANPRM, in preparing the NPRM, the deliberations of the Presidential Commission for the Study of Bioethical Issues (the Commission) were taken into account. Consideration was also given to public comments received on the request for information issued by the Commission on March 2, 2011, that sought

public comment on the current federal and international standards for protecting the health and well-being of participants in scientific studies supported by the federal government.[92]

These suggested revisions to the Common Rule may affect other regulatory protections, such as the other subparts of the HHS human subjects protection regulations in 45 CFR part 46 (Subparts B, C, and D, which deal with particular populations of vulnerable subjects, and Subpart E which addresses registration of IRBs), FDA regulations, and the HIPAA Privacy Rule (45 CFR Parts 160 and 164, Subparts A and E). It is contemplated that other regulatory provisions implicated by the changes to the Common Rule may need to be harmonized, to the extent appropriate, with any final regulations modifying the Common Rule, through rule modification or guidance. Additionally, guidance and other information would also be revised and/or written to the extent necessary and appropriate.[93]

B. ANPRM Issues and Public Comments Related to Improving Protections

1. Expanding the Scope of the Common Rule

The ANPRM asked for public comments regarding two potential changes to the regulations at §__.101. The first would subject unaffiliated IRBs (IRBs that are not operated by an FWA-holding institution) that review research covered by the Common Rule to the requirements of the Common Rule. The second would extend the scope of research covered by the regulations.

[92] 76 FR 11482 (Mar. 2, 2011).
[93] Research not subject to the Common Rule may still be subject to FDA regulation or the HIPAA Privacy Rule.

Holding Unaffiliated IRBs Directly Accountable for Compliance with Certain Regulatory Requirements: To address institutions' concerns about OHRP's practice of enforcing compliance with the Common Rule through the institutions that are engaged in human subjects research, the ANPRM asked for comments on making appropriate changes to the Common Rule enforcement procedures so external IRBs are held directly accountable for compliance with certain regulatory requirements.[94]

Based on public comments received to a 2009 ANPRM[95] on the issue of IRB accountability, the July 2011 Common Rule ANPRM considered adding a new provision that would give Common Rule departments and agencies the authority to enforce compliance directly against IRBs that are not affiliated with an institution that has an assurance registered with HHS. This provision would not extend the scope of research that is covered by the regulations; rather, it would expand the scope of those entities subject to compliance oversight.

Some public commenters responding to the 2011 ANPRM cautioned that extending compliance oversight to unaffiliated IRBs might serve as a disincentive for some IRBs to be the IRB of record for cooperative research. A majority of commenters expressed an opposing view; that is, holding external IRBs directly accountable for compliance with the regulations would increase the comfort level of institutions in accepting the regulatory review of an external IRB.

[94] See, e.g., the proposal on IRB accountability released by OHRP in 2009, at http://www.hhs.gov/ohrp/newsroom/rfc/com030509.html.
[95] 74 FR 9578 (Mar. 5, 2009).

Extension of Common Rule to Domestic Sites Funded by Common Rule Agencies: The ANPRM asked the public to consider a regulatory option to partially fulfill the goal of extending Common Rule protections to all human subjects research in the United States. The discussed policy would require domestic institutions that receive some federal funding from a Common Rule agency for nonexempt research with human subjects to extend the Common Rule protections to all human subjects research studies conducted at their institution.

Although supporting the principle that all human subjects research regardless of funding source should be conducted ethically, public commenters generally expressed concern and caution about the ANPRM consideration for a variety of reasons. Behavioral and social science researchers thought that this approach would unnecessarily bring less-than-minimal-risk research funded by non-federal sources (e.g., surveys or observational studies supported by the nonprofit sector) under burdensome regulatory requirements while not enhancing protections. Some commenters argued that the increased regulatory burden that would ensue was not warranted and would shift scarce oversight resources to review of research studies that are generally non-problematic and frequently supported by non-federal funds, such as some student or institutional research.

Others argued that such a change was an overreach of federal oversight and constituted an unfunded mandate. Commenters from large academic research institutions felt that this change inappropriately focused heavily on academic institutions, which generally extend protections to all human subjects research at their institution, even if they have not "checked the box"[96] on their

[96] The FWA covers all nonexempt human subjects research at the submitting institution that is HHS-conducted or –supported, or funded by any other federal department or agency that has adopted the Common Rule and relies upon the FWA. It is not project specific. Domestic institutions may voluntarily extend their FWA (and thus a Common

FWA indicating that they do so. They argued that such a change would not reach those institutions already operating outside the federal research system and would limit flexibility in making risk-based determinations about the levels of review required.

Industry also expressed concern about having to comply with two sets of regulations, that is, FDA regulations at 21 CFR Parts 50 and 56 as well as the Common Rule. The ANPRM did not clarify that the changes under consideration would not require compliance with the Common Rule of non-federally funded research subject to regulation by FDA. However, there might continue to be research that would be subject to both sets of regulations involving federal funding of research concerning an FDA-regulated product.

Those commenters who supported a formal extension of the regulations cited the need to have one set of standards for all research, regardless of funding source; however, many noted that absent legislation covering all human subjects research conducted in the United States, it would be difficult to cover all research through a regulatory approach alone—gaps would still remain.

2. Safeguards for Information

Definition of Private Information and Applying the HIPAA Standards of "Identifiability" to Research Governed by the Common Rule: The ANPRM suggested that the definition of

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Rule department or agency's regulatory authority) to cover all human subjects research at the submitting institution regardless of the source of support for the particular research activity. See Office for Human Research Subject Protections. (2011, June 17). What research does the Federalwide Assurance (FWA) cover? Retrieved from Frequently Asked Questions: http://www.hhs.gov/ohrp/policy/faq/assurance-process/what-research-does-fwa-cover.html

"identifiability" in the Common Rule be modified to better harmonize it with other regulatory definitions of "identifiability" within HHS. The ANPRM considered adopting for purposes of the Common Rule the HIPAA Privacy Rule's standards of what constitutes individually identifiable information, a limited data set, and de-identified information, in order to address inconsistencies regarding these definitions and concepts between the HIPAA Privacy Rule and the Common Rule. In addition, the ANPRM indicated that a prohibition on the re-identification of de-identified information (as defined in the HIPAA Privacy Rule) was being considered.

Private information is not considered to be identifiable under the Common Rule if the identity of the subject is not or may not be "readily ascertained" by the investigator from the information or associated with the information. In contrast, under the HIPAA Privacy Rule, health information is de-identified and thus exempt from the Rule only if it neither identifies nor provides a reasonable basis to believe that the information can be used to identify an individual. The HIPAA Privacy Rule provides two ways to de-identify information: (1) a formal determination by a qualified expert that the risk is very small that an individual could be identified; or (2) the removal of all 18 specified identifiers of the individual and of the individual's relatives, household members, and employers, as long as the covered entity has no actual knowledge that the remaining information could be used to identify the individual (45 CFR 164.514(b)).

The HIPAA Privacy Rule addresses some informational risks by imposing restrictions on how individually identifiable health information collected by health plans, health care clearinghouses, and most health care providers ("covered entities") may be used and disclosed, including for research. In addition, the HIPAA Security Rule (45 CFR Parts 160 and Subparts A and C of part

164) requires that these entities implement certain administrative, physical, and technical safeguards to protect this information, when in electronic form, from unauthorized use or disclosure. However, the HIPAA Rules apply only to covered entities (and in certain respects to their business associates), and not all investigators are part of a covered entity. Moreover, the HIPAA Rules do not apply specifically to biospecimens in and of themselves.

A majority of the public commenters strongly opposed the ideas discussed in the ANPRM regarding the definition of "identifiability". Many indicated that the HIPAA Privacy Rule's more stringent standard of identifiability would expand what is considered identifiable for purposes of the Common Rule and thus greatly impede generally low-risk research without adding meaningful protections for human subjects. In particular, they asserted that the HIPAA standards were created to protect against disclosure of health information contained in medical records. As such, commenters argued, they are not appropriate for many types of research that would be covered by the Common Rule (e.g., behavioral and social science research). Others said this would be an extreme change in response to an as yet unidentified or clear problem. Commenters said that the information most at risk for inappropriate disclosure is the type of private health information that is already protected under the HIPAA Rules. Commenters feared that such a change in policy, while "harmonizing" the Common Rule certain HIPAA standards, would create inordinate burdens in terms of new documentation requirements and result in a requirement to apply the HIPAA standards to all types of research, regardless of the level of risk.

Several commenters expressed concern about a prohibition against re-identifying de-identified private information (as defined by HIPAA), noting that sometimes it will be appropriate for

investigators to re-identify such information, for example, to return research results that have clinical relevance to the subjects. Also, some commenters noted that some research is specifically designed to test strategies for re-identifying de-identified (as defined by HIPAA) information, so an absolute prohibition against re-identification would halt such research.

Protecting Information: The ANPRM suggested establishment of mandatory data security and information protection standards for all studies that involve the collection, generation, storage, or use of identifiable or potentially identifiable information that might exist electronically or in paper form or contained in a biospecimen. It put forward the idea that these standards might be modeled after certain standards of HIPAA Rules and asked a series of questions about how best to protect private information.

Some public comments reflected confusion about the focus of the suggested standards and whether they would apply to information or biospecimens that were not individually identifiable. Although most commenters confirmed the need to protect the privacy and confidentiality of information of human subjects in research, a majority expressed serious concerns about the merits of requiring all investigators to meet standards modeled on certain HIPAA standards, such as those in the HIPAA Security Rule. Most commenters expressed the opinion that certain HIPAA standards are not well suited to some research of various kinds carried out by investigators not subject to the HIPAA Rules. Some commenters claimed that the HIPAA privacy standards do not adequately protect individuals' information. Many commenters claimed that standards modeled after certain HIPAA standards would be unnecessarily burdensome for

studies in the behavioral and social sciences where the data are often less sensitive than health information.

Some comments maintained that HIPAA like standards would not always be suitable for the variety of research methods and procedures for the collection and storage of information in research activities not subject to the HIPAA Rules. Some commented that certain HIPAA standards would not be suitable because of the location of the research activity, or because the kind of institution supporting the research was significantly different from a covered entity. Others thought the HIPAA standards create confusion and complications for investigators and institutions that would increase if standards modeled on certain HIPAA standards were applied across the board. At the same time, regardless of the specific standards to be employed under this approach, several commenters noted that the additional administrative burden that might be created by establishing a data security and information protection system could be offset by the decreased time and attention IRBs would have to invest in reviewing every study that required data or biospecimen protections. They also noted that many institutions already have required data and biospecimen protection systems in place.

Some commenters noted that expansion of some of the exemption categories could only be ethically acceptable if those research activities were subject to a requirement for data security and information protection, because information collected for some research studies would no longer be collected under a research plan approved by an IRB. With regard to an absolute prohibition against re-identifying de-identified data, many commenters expressed concern, and provided reasons why re-identification might be valid or even desirable, including the need to

return clinically relevant research results to an individual. For example, if the research uncovers information that might have important clinical significance for an individual, re-identification could be used so that the individual could get care. In addition, they pointed out that the current Common Rule requires investigators that re-identify nonidentified private information as part of a research study to comply with the current Common Rule regulatory requirements.

3. Improving Informed Consent, Including Requiring Informed Consent for Research Use of Biospecimens and the Use of Broad Consent for Secondary Research Use of Biospecimens and Information

The public was asked to comment on: the length and complexity of informed consent forms; additional information, if any, that should be required by the regulations to assure that consent forms appropriately inform subjects about alternatives to participation, as well as whether or not there should be modifications or deletions to the required elements; whether subject comprehension should be assessed, and if so, under what circumstances; whether changes to the Common Rule would necessitate conforming changes to the authorization requirements of the HIPAA privacy requirements; and whether additional requirements in the consent process are warranted, such as financial disclosures by investigators. The ANPRM also requested comment on the need for regulation of consent for the following: research use of biospecimens collected for clinical purposes, consent for research use of pre-existing data, and consent to secondary research use of data and biospecimens.

Consent for Research Use of Biospecimens and Information Generally:

The ANPRM also requested comment on the value of generally requiring written consent for research use of any biospecimens collected for *clinical* purposes after the effective date of the new rules (such as research with excess pathology biospecimens). Such consent could be obtained by use of a brief standard consent form agreeing to generally permit future research. This brief consent could be broad enough to cover all biospecimens to be collected related to a particular set of encounters with an institution (e.g., hospitalization) or even to any biospecimens to be collected at any time by that institution. The general rule as discussed in the ANPRM would be that a person needs to give consent, in writing, for research use of their biospecimens, though that consent need not be study-specific, and could cover open-ended future research.

The ideas presented in the ANPRM would be a substantial change from the current Rules in several ways. First, the current Rules allow research without consent when a biospecimen is used for research under conditions where the researcher does not possess information that would allow them to identify the person whose biospecimen is being studied. Thus, biospecimens collected as part of a non-research protocol (e.g., clinical care) could be made nonidentified and used in research as long as the researcher cannot identify the source of the biospecimen. The ANPRM consideration would no longer allow that to occur, generally requiring researchers to obtain consent for research use of clinical biospecimens, even if nonidentified. A waiver of consent under limited circumstances was contemplated in the ANPRM, but no specific waiver criteria were discussed.

A majority of the commenters opposed the ANPRM's suggested requirement to have consent for research use of all biospecimens, regardless of identifiability, on both administrative and ethical

grounds. Administrative reasons for opposition to the suggested consent requirements included the prohibitive costs to collect, log, and track consent status of data and biospecimens, and the considerable administrative efforts that would be required to keep track of the consent status. Commenters opposed to the suggested consent requirements on ethical grounds cited increased privacy risks to subjects arising from the need to maintain links between the consent documents and the biospecimens or data in order to ensure that any restrictions on the research use of such resources were honored. They also expressed their belief that convincing evidence of harm caused by research use of nonidentified clinical biospecimens without consent is lacking, especially when considering the public health benefit of such use, and noting that they were not convinced that the principle of autonomy outweighs or trumps the principle of beneficence. Some patient advocacy organizations also expressed concerns about the consequences of requiring consent for the use of nonidentified biospecimens. Yet, most of the comments from individual members of the public strongly supported consent requirements for use of their biospecimens, regardless of identifiability, or data.

Many commenters expressed the opinion that the existing regulatory framework is adequate and that current practices should be maintained, stressing that the research use of nonidentified data or biospecimens does not involve risk to the research participant. One commenter noted that "In our extensive professional experience working with biospecimens on a daily basis, the current system has worked well and has greatly enriched the opportunity for discoveries that were unknown at the time of collection and when research does not require subject identification or involve patient risk." In contrast, some commenters supported the idea of requiring consent for research use of all biospecimens, with one commenter noting simply that "research use of data

initially collected for non-research purposes should always require informed consent." Commenters particularly noted concerns about imposing consent requirements on the use of biospecimens already collected—that is, not grandfathering in such resources—especially if these biospecimens are nonidentified. Requiring that consent be obtained for the use of these materials could result in their being rendered useless for research, which would represent a cost of its own in terms of lost opportunity. This concern was based on the practical limitations involved in obtaining consent for biospecimens that were de-identified in the past, given that it may not be possible to re-contact the original source.

The objections raised by the commenters about the possible adverse consequences of requiring consent for the use of nonidentified biospecimens—including, in particular, the proposition that such a change might significantly compromise an important and relatively low-risk area of research—resulted in suggestions in the comments that this should be systematically assessed before suggesting any new rules. In fact, several commenters suggested that data be collected on the cost and feasibility of instituting such a requirement before revising the Common Rule.

Consent Rules for Research Use of Pre-existing Data: The ANPRM asked for comments on revising the consent rules for research use of data previously collected for purposes other than the suggested research study. First, if the data were originally collected for non-research purposes, then, as is currently the rule, written consent would only be required if the researcher obtains information that identifies the subjects. There would accordingly be no change in the current ability of researchers to conduct such research using de-identified data or a limited data set, as such terms are used in the HIPAA Rules, without obtaining consent.

Second, if the data were originally collected for research purposes, then consent would be required regardless of whether the investigator obtains identifiers. Note that this would be a change with regard to the current interpretation of the Common Rule in the case where the researcher does not obtain any identifiers. That is, the allowable current practice of telling the subjects, during the initial research consent, that the information they are providing will be used for one purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented, would not be allowed.

Consent to Secondary Research Use of Data and Biospecimens through Broad Consent: The ANPRM suggested that consent for the use of biospecimens or data could be obtained using a standard, short form, in which the subject could be asked to provide broad consent, that is, consent for a variety of potential future uses of their biospecimens or data. The requirement for consent could be waived in certain circumstances. These changes would apply only to biospecimens and data collected after the effective date of a new final rule.

Public comments revealed variable opinions on this issue. Several commenters indicated that there is no need for additional regulations, with one university stating that it "strongly opposes more restrictive regulations about the use of these biospecimens and sees no need to change the current regulations, even or perhaps especially in the case of secondary data analysis." Other commenters opposed broad consent, stating that researchers and clinicians should obtain specific consent from individuals for each research project. This opposition was made on the ethical grounds that because individuals are not fully informed of specific research purposes for broad

consent, they can never be truly informed about the use of their data. In contrast, other commenters expressed clear support for general consent for secondary research use of biospecimens and data collected during research to exempt the research from IRB review, noting that "we support the suggestion in the ANPRM to encourage general consent for the secondary research use of biospecimens and data and where this is not obtained IRB review is required." Other commenters favored requiring IRB review over permitting the use of a broad consent to approve secondary research use of identifiable data or biospecimens. These commenters believed that IRB consideration of consent requirements for individual research studies was more protective of human subjects than the ANPRM suggestions to permit broad consent for future use.

With regard to the burden of obtaining consent for the research use of de-identified biospecimens, this requirement could be less burdensome than anticipated due to the ANPRM's suggested allowance of broad consent. While the ANPRM suggested requiring consent for the use of biospecimens, it suggested allowing a one-time, broad consent for future uses to be obtained with a template form which, if used without changes, would not require IRB review, and could be obtained at the same time as the initial research or clinical consent. Some commenters, particularly patients and patient advocacy groups, expressed concern about the burden of re-consenting patients for broad consent after biospecimens were collected.

Several commenters suggested that data be collected on the cost and feasibility of instituting such a requirement before revising the Common Rule.

In most instances, the consent requirements described above would have been met at the time that the biospecimens or data were initially collected, when, under the ANPRM the subject would have signed a standard, brief general consent form allowing for secondary research. This brief consent could be broad enough to cover all data and biospecimens to be collected related to a particular set of encounters with an institution (e.g., hospitalization) or to any data or biospecimens to be collected at any time by the institution, even as part of a research protocol.

The ANPRM suggested that this standardized broad consent form would permit the subject to say no to all future research. In addition, the ANPRM acknowledged that there are likely to be a handful of special categories of research with biospecimens that, given the unique concerns they might raise for a significant segment of the public, could be dealt with by check-off boxes allowing subjects to separately say agree or disagree to that particular type of research.

Further, the ANPRM suggested that the current prohibition that participation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using a biospecimen would be maintained. With regard to the secondary research use of pre-existing data, on those occasions when oral consent was acceptable under the regulations for the initial data collection, the ANPRM envisioned that subjects would have typically provided their oral consent for future research at the time of the initial data collection; a written consent form would not have to be signed in that circumstance.

The ANPRM suggested that these changes would only be applied prospectively, not retrospectively. In other words, they would only apply to biospecimens and data that are

collected after the effective date of the new rules. It also noted that there would be rules that would allow for waiver of consent under specified circumstances, though those conditions would not necessarily be the same as those for other types of research.

Improving Consent Forms and Modifying the Required Elements of Consent: Public comments were largely in favor of finding ways to improve consent forms. However, commenters cited several systemic concerns that could be obstacles to shortening and simplifying forms, such as regulatory, legal, and institutional requirements, and the complexity of some studies. Of those responding to questions about the causative factors, blame for making forms long and complex was shared by sponsors of clinical trials, IRBs, regulatory agencies, and institutional legal counsel. The types of information cited as contributing to the excessive lengths of forms included the requirement to describe all reasonably foreseeable research risks and the complexity of study procedures. There was no consensus on how to better explain alternatives to research participation and few comments were submitted on this topic.

Commenters offered a few suggestions for modifying or deleting the required elements of consent, such as removing boilerplate language that only protects institutions and research sponsors, as well as removing some of the required elements for minimal risk research. However, many felt that guidance, rather than regulatory change, would better improve the development of consent forms. Although many commenters noted the need for shorter and more comprehensible consent forms, most felt that the required elements of consent articulated in the Common Rule are sufficient. Commenters overwhelmingly supported the goals articulated in the ANPRM, but cautioned against an overly prescriptive or rigid approach to consent forms.

However, several commenters requested guidance on what might be included in a consent form for future research use of identifiable information and identifiable biospecimens to ensure that such forms satisfied the consent requirements of the Common Rule.

A majority of commenters supported the development of regulations or guidance designed to encourage assessment of the extent to which human subjects comprehend consent forms, at least for certain types of higher risk studies or certain types of subject populations. Others argued that the regulations at §___.116 already contain language implying the need to ensure comprehension through the use of the terms "legally effective informed consent" and "language understandable to the subject."

Finally, many commenters supported making changes to HIPAA authorization requirements, as necessary to conform to provisions of the Common Rule. In addition, most commenters were supportive of requiring investigators to disclose in consent forms certain information about the financial relationships they have with study sponsors.

Criteria for Waiver of Consent: The ANPRM asked whether changes to the regulations would clarify the current four criteria for waiver of informed consent and facilitate their consistent application. Few comments were received on this topic although many commenters expressed support for clarifying the key terms through guidance or altering the criteria. In particular, most comments on this topic noted the confusion that IRBs face when trying to understand the meaning of the terms "practicable" and "adversely affect the rights and welfare of subjects." Some commenters expressed the opinion that the waiver criterion concerning rights and welfare

should be interpreted to include reference to rights conferred by other federal laws or regulations, state or local laws, or laws in other countries where research is to be conducted. Some comments reflected concerns about privacy or security.

The ANPRM also asked for comments on the information investigators should be required to provide to prospective subjects in circumstances where the regulations would permit oral consent. Additional questions focused on whether there are additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent, and whether there are types of research in which oral consent without documentation should not be permitted. There were few responses to these questions and no common themes or consensus among those submitted. However, several commenters pointed to the need to consider community norms throughout the consent process, including its documentation.

4. Improving the Collection and Analysis of Adverse Event Reports

The ANPRM asked the public to consider a number of changes to improve the current system for the real-time prompt collection of data regarding adverse events. The changes that the ANPRM stated were under consideration were intended to simplify and consolidate the reporting of information that is already required to be reported by an investigator, and not to expand the information that has to be reported. In addition to these changes, the ANPRM indicated that the Federal Government was also considering creating a central web-based repository to house a great deal of the information collected through the portal.

Although a number of commenters applauded the goal of easing and harmonizing reporting requirements, most expressed concerns about collecting data on unanticipated problems and adverse events in a central database. Those who supported the concept of centralized reporting asked for more detail on what such a system would entail. More specifically, several commenters noted that IRBs sometimes struggle with what should be reported and with distinguishing between the Common Rule term "unanticipated problems" and the FDA term "adverse events." Commenters noted that under the Common Rule at §__.103(b)(5), each institution determines through its own policies the procedures for reporting unanticipated problems to department or agency heads. As a result, there is no standardized definition of "unanticipated problems," so each institution may be reporting different events. Commenters also sought better guidance on those terms and encouraged agencies to clarify meanings and reporting requirements.

Commenters stated that a standardized, streamlined set of data elements, a single web-based reporting tool that facilitates delivery to agencies and oversight bodies, and harmonized Federal agency guidance would simplify the process. However, many expressed skepticism that harmonization across Federal agencies could occur.

With regard to a centralized database, many commenters expressed concerns regarding the value in terms of cost and time with compiling such data, gleaned from diverse studies and sources, in order to conduct an integrated analysis. They commented that it is unclear how the data would be useful beyond a specific study and unclear who would have access to the data and how it would

be managed and interpreted to better inform the regulatory process. Commenters asked, if the data reporting is real-time, who is expected to develop such a system and review incoming data to coordinate the appropriate response? Many commenters questioned the validity of data collected in such a generic manner and the ability to draw generalizable conclusions based on data collected from varied sources and contexts. Several commenters said that before implementing such a central repository, a thorough cost-benefit analysis should be conducted regarding strengths and limitations of similar data repositories. Until the utility of such a centralized system could be demonstrated, especially when compared to the current decentralized system, many felt the burden of creating such a system would not be counterbalanced by the benefit of added protections. Along these lines, commenters also questioned the utility of counting how many human subjects are enrolled in trials, stating that this would not be a meaningful way to develop risk estimates.

Many commenters cited the adequacy of current reporting systems, despite the need for improvement. Centralized reporting of adverse events would represent a dramatic change from how events are collected and reported now. For example, sponsors of clinical trials are responsible for continuously monitoring their trials, adverse events must be reported to sponsors, and new reporting would not substitute for reports to sponsors. In addition, under FDA regulations, when applicable, safety information from non-U.S. clinical trials may need to be reported. Moreover, sponsors and funding agencies probably would not rely on extracting information from a federal database as the source of information to meet all of their safety oversight obligations and would likely still require investigators to complete adverse event case report forms as well as rely on the use of Data Safety Monitoring Boards. Commenters also

raised concerns that the use of an electronic centralized reporting system could be a substantial burden on investigators, may potentially decrease investigators' willingness to participate in trials, and may encourage the conduct of studies outside the regulations. If reporting systems were now required to also gather and store unanticipated problems in addition to adverse events, commenters said the system would become unwieldy, run the risk of creating long lag times in analysis, and draw low risk events into a system that should be focused on the highest risk studies. Several commenters recommended that more efforts be made to improve current reporting systems, particularly ClinicalTrials.gov.

Based on the public comments, the NPRM does not pursue a centralized reporting system and thus this issue is not addressed further. OHRP will continue to engage in discussions with FDA and Common Rule departments and agencies regarding clarifying reporting terms and requirements.

5. Identifiability of Biospecimens

The ANPRM suggested that, regardless of what information is removed, it is possible to extract DNA from a biospecimen itself and potentially link it to otherwise available data to identify individuals. In addition, irrespective of whether biospecimens are considered individually identifiable, the ANPRM sought comment on whether the regulations should be changed to respect individuals' interest in being able to decide whether their biospecimens would be available for research, even if the biospecimen was not associated with any identifiable information. Consequently, it asked for public comment on the value of categorizing all research

involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information.

The ANPRM asked whether some types of genomic data should be considered identifiable and, if so, which types (e.g., genome-wide single nucleotide polymorphism [SNP] analyses or whole genome sequences). It also asked whether human biospecimens should be considered inherently identifiable. A majority of commenters opposed changing the Common Rule to consider all biospecimens identifiable as defined by the existing regulations at §__.102(f)(2) (and thereby categorizing their use as research involving a human subject), and expressed concern that doing so would significantly slow advances in research and human health. Several commenters noted that, although it is theoretically plausible to identify a person based on his or her biospecimen, the likelihood remains remote enough to argue against the presumption that the sources of all biospecimens are identifiable and cited a study showing that the risk of re-identification from a system intrusion of databases was only 0.22%.[97] Other commenters cited the administrative burden that would be exacted should such an interpretation be implemented, without sufficient evidence that such an interpretation would be reasonable or enhance protections.

Commenters were mostly concerned with the cost and burden that would be imposed by the requirement to obtain consent. Commenters anticipated these costs to include obtaining consent from participants and the administrative efforts required to keep track of the consent status of biospecimens. Most commenters did not provide detailed cost estimates with their comments;

[97] Kwok P et al. Harder Than You Think: A Case Study of Re-Identification Risk of HIPAA-Compliant Records. NORC at The University of Chicago and Office of the National Coordinator for Health Information Technology. 2011. http://www.amstat.org/meetings/jsm/2011/onlineprogram/AbstractDetails.cfm?abstractid=302255

data are specifically requested in response to this NPRM. In addition, estimates of the type and number of studies that could not be pursued using existing samples and data because of the absence of sufficient consent are requested. Comment is also sought on the value to the public and research participants of being asked their permission for research use of their data and specimens.

Several commenters also stated that if the Common Rule were modified such that all biospecimens were covered under the rule regardless of their identifiability, there still might be some activities involving biospecimens or types of biospecimens that should be considered exempt or "excused." Suggestions included:

- Identifying markers for cancer prognosis or prediction of response to cancer therapy, or identifying cancer molecular targets (molecular research)
- Basic science research (including analysis of biological processes)
- Research of rare conditions and diseases
- Pediatric research
- Research with samples that lack potentially identifying information, such as serum or plasma not containing DNA
- Biospecimens lacking nucleic acids (such as certain red blood cells, expiratory gases)
- Blood culture bacteria
- Bacterial and viral specimens (this was listed in a comment as a public health issue)
- Protein analysis

- Statistical method development (to the extent that this development is related to biospecimens)
- New molecular methods to detect infectious agents
- Use of specimens to develop and validate new assays for infectious agents
- Archival paraffin blocks

One commenter also suggested that the Rule could propose a definition for biospecimen such that the term does not include sample types that lack DNA.

In addition, some commenters noted that the recommendation to require consent might privilege the Belmont Report's principle of autonomy over the principle of justice, because requiring consent could result in lower participation rates in research by minority groups and marginalized members of society. The literature on consent rates in studies involving biospecimens suggests that while minority consent rates in some cases may be lower than non-minorities, when asked to consent, minority consent rates are still higher than projected.[98,99,100] Furthermore, better communication and community engagement with members of specific minority groups is needed to understand and address concerns related to research, and these measures could substantially improve participation rates. An increase in trust and partnership is likely to increase participation rates; using their samples and data without permission will hinder true partnership.

[98] Pentz RD et al. Research on Stored Biological Samples: Views of African American and White American Cancer Patients. American Journal of Medical Genetics, Part A. 2006 Apr 1; 140(7):733-9.
[99] Chen DT et al. Research With Stored Biological Samples; What Do Research Participants Want? Archives of Internal Medicine. 2005 Mar 28; 165(6):652-5.
[100] Scott et al. Biospecimen Repositories: Are Blood Donors Willing to Participate? Transfusion. 2010 September; 50(9): 1943-1950.

C. ANPRM Issues and Public Comments Related to Reducing Regulatory Burden

1. Activities Excluded from the Policy

The ANPRM asked questions about the definition of research and whether various activities should be excluded from the Common Rule, either by changing the definition of research or by adding exemptions, or both. The ANPRM sought comment on whether and, if so, how, the Common Rule should be changed to clarify whether quality improvement activities, program evaluation studies, or public health activities are covered. It also asked whether there are specific types of studies for which the existing rules are inappropriate. If so, comments were sought on whether this problem should be addressed through modifications to the exemption categories, or by changing the definition of "research" used in the Common Rule to exclude some of these studies, or a combination of both.

If the definition of research were to be changed, public comment was sought on how excluded activities should be defined (e.g., "quality improvement" or "program evaluation"). With regard to quality improvement activities, the public was asked to comment on whether it might be useful to adopt the distinction made by the HIPAA Privacy Rule, which distinguishes between "health care operations" and "research" activities, defining "health care operations" to include, among other activities, "conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities."

A majority of public comments supported excluding the following from the regulatory requirements: quality improvement activities, public health activities, and program evaluation. Many of these commenters argued that the public benefits resulting from these activities justified their practice, particularly given the generally low risk involved. Some argued that for some legally mandated activities designed to accomplish a public good, it would be inappropriate for IRBs or individuals to be able to impede or thwart the execution of those mandated activities. A majority of comments also favored distinguishing between research and health care operations, as such terms are defined in the HIPAA Privacy Rule, and excluding the latter from the policy. Some commenters noted that people involved in these various activities are protected in other ways, and alluded to the sorts of measures that provide a measure of protection. Others suggested that any exclusions should be limited to data collection and analysis activities, or to activities below a certain threshold of risk (i.e., minimal risk). A minority of comments objected to these exclusions, arguing that these activities represent encroachments on their individual rights and privacy, and that oversight in accordance with the Common Rule requirements would be more protective.

The overwhelming majority of public comments responding to the question about excluding specific fields of study from the regulatory requirements of the Common Rule supported explicitly excluding certain activities from the definition of research versus modifying the exemption categories. The overwhelming majority of these comments focused on oral history. Some of the comments were virtually identical and appear to have been coordinated. Many of the comments reflected the view that the Common Rule was not designed or intended to include oral

history activities, and that the ethical codes pertaining to oral history procedures are not consistent with the application of ethical principles reflected in the Common Rule.

A smaller number of similar comments were submitted with respect to various humanities disciplines and journalism. A significant minority of commenters opposed the exclusion of any fields of study, arguing that the activity itself rather than the academic discipline or training of the investigator should be the basis for the assessment of whether the activity should be excluded. Some of the commenters recommended that the definition of research be focused more explicitly by being limited to "biomedical and behavioral research," in accordance with the statutory provision underlying the Common Rule. A significant number of commenters recommended that guidance should be issued to clarify how the definition of research should be applied, with cases and explanations.

2. Research Exempt from IRB Oversight

Exemption Determination: The ANPRM discussed a mechanism to (1) register exempt research, and (2) audit a small but appropriate portion of such research, which would still be subject to other regulatory protections such as the suggested data security and information protection standards and certain consent requirements. The term "excused" rather than "exempt" was recommended to describe these categories of research, because they are not entirely exempt from oversight.

The ANPRM discussed a tracking mechanism to enable institutions to assure that such research meets the criteria for inclusion in the suggested "excused" categories. The original recommendations would require investigators to register their study with an institutional office by completing a brief form, thus eliminating the current practice of not allowing investigators to begin conducting such studies until a reviewer had determined it met the criteria for excused research. This would make the institution aware of key information about the research (such as the purpose of the research and the name of the study's principal investigator), without also requiring that the activity undergo a review that, if not done in a timely manner, could slow the research without adding any significant protection to subjects. In addition the institution could choose to review some of the submissions at the time they are filed and, if deemed appropriate, require that the study be sent for expedited review or, in rare cases, convened IRB review. It would be made clear that the regulations would not require, and in fact, would discourage, having each of these registration forms undergo a comprehensive administrative or IRB review prior to commencing the study or even afterward.

The auditing requirement was intended to encourage institutions to use the regulatory flexibility suggested for the "excused" categories of research. The auditing requirement would have provided institutions with information needed to assess their compliance with the new "excused" categories without unnecessarily subjecting all such research to either prospective review, or even routine review sometime after the study is begun. Note that currently, OHRP recommends that there be some type of review by someone other than the investigator to confirm that a study

qualifies as exempt, and many institutions do impose such a requirement even though such a requirement is extra-regulatory.[101]

The ANPRM also asked whether this research should be called "excused" or some other term, whether it was acceptable for investigators to independently determine whether their research was excused, whether review of all registrations should be required, and whether there should be a time limitation or waiting period before excused research could begin. The ANPRM also asked whether it was appropriate to require institutions holding an FWA to conduct retrospective audits of a percentage of the excused studies to make sure they qualify for inclusion in an excused category, and if so, how such audits should be conducted.

Commenters overwhelmingly expressed concerns about adopting the term "excused" to describe this area of research and suggested the term "registered" should such a system be adopted. Commenters recommended the term "registered" because such studies would not be exempt or excused from other requirements, such as compliance with data and security provisions as well as, in certain circumstances, informed consent requirements. In general, commenters were not necessarily opposed to the concept of registration but sought further information on what this process would entail.

Public commenters also expressed concerns about allowing an investigator to independently make the determination that his or her research is exempt. Other commenters suggested that this practice would be acceptable for some investigators, whose research is well known to IRB

[101] Office for Human Research Protections. (2011, January 20). Exempt Research Determination FAQs. Retrieved from Frequently Asked Questions About Human Research: http://www.hhs.gov/ohrp/policy/faq/index.html,

members, and is clearly within an exempt category. The ANPRM noted concerns that some exempt research was unnecessarily delayed by requirements of some institutions to review the research to make an exemption decision.

Several institutions reported that they already as a matter of policy require investigators to submit exempt studies to the IRB, not necessarily for full board review, but to ensure that the exempt determination is valid. These decisions typically are made by the IRB administrator and never involve full review unless there is concern about the exemption status. Thus, they felt the registration requirement was unnecessary and would add new administrative burdens for research already considered low risk.

Other commenters, such as investigators conducting research currently considered exempt, were strongly opposed to a registration requirement because it would add a new burden to conducting less than minimal risk and exempt research. In addition, commenters raised concerns about the administrative burden and need for a retrospective audit system of registered research.

Exemption Categories: The ANPRM considered revising the regulations regarding studies currently considered exempt by expanding the current exemption category 2 (research involving educational tests, surveys, focus groups, interviews, and similar procedures, found in the current Rule at §__.101(b)(2)) to include all studies involving educational tests, surveys, interviews, and similar procedures so long as the subjects are competent adults, without any further qualifications. It also considered adding a new category for certain types of behavioral and social science research that goes beyond using only survey methodology, but nonetheless involves only

specified minimal risk procedures, so long as the subjects are competent adults (but subject to the data security and information protection standards). The term "competent" as used in the ANPRM referred to adults who would be able to provide "legally effective informed consent," as currently required by §__.116.[102]

The ANPRM also considered whether to include on the list of exempt studies certain types of social and behavioral research conducted with competent adults that would involve specified types of benign interventions commonly used in social and behavioral research, that are known to involve virtually no risk to subjects, and for which prior review does little to increase protections to subjects. These would be methodologies that are familiar to people in everyday life and in which verbal or similar responses would constitute the research data being collected. For example, an investigator might ask subjects to watch a video, read a paragraph, or solve puzzles, and then ask them some questions to elicit word associations or time performance of activities. The specific methodologies might be spelled out in regulations, or they might be promulgated via a periodic mechanism to announce and update lists similar to the list that is published for activities that may be reviewed by an IRB using the expedited review procedures.[103]

A majority of commenters supported the ANPRM discussion on expanding current exemption category 2 (current Rule at §__.101(b)(2)) by eliminating the limitations related to the recording

[102] Informed consent is legally effective if ,in part, it is both obtained from the subject or the subject's legally authorized representative and documented in a manner that is consistent with the HHS protection of human subjects regulations and with applicable laws of the jurisdiction in which the research is conducted. See Office for Human Research Protections. (2011, January 20). What is the meaning of "legally effective informed consent?". Retrieved from Frequently Asked Questions: http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-is-legally-effective-informed-consent.html

[103] 63 FR 60364 (Nov 9, 1998). Also available at, http://www.hhs.gov/ohrp/policy/expedited98.html.

of identifiable information and the harm that could result if a subject's responses were disclosed. However, many commenters were opposed to the requirement that subjects be "competent adults" in order for the expanded exemption to apply, asking whether tests of competency would be required for such research to proceed.

Many commenters also supported adding another exemption category of research for certain types of social and behavioral activities, conducted with competent adults, that would involve specified types of benign interventions beyond educational tests, surveys, focus groups, interviews, and similar procedures that are commonly used in social and behavioral research, that are known to involve virtually no risk to subjects, and for which IRB review does little to increase protections for subjects.

The ANPRM asked questions about whether the current limitations specified in exempt category 4 (research involving the use of existing information or biospecimens, §__.101(b)(4) in the current Rule) should be eliminated. Specifically, the ANPRM suggested that the category would be revised to eliminate the word "existing." With this elimination, the exemption would be broadened to cover the use of information or biospecimens that were or will be collected for purposes other than the suggested research, rather than requiring that all of the information or biospecimens already exist at the time the study is suggested for exemption.

The ANPRM also discussed whether research involving only the use of data or biospecimens collected for other purposes, even if the investigator intends to retain identifiers, should come within a new exemption category; studies that include a plan to provide individual research

results to subjects would not qualify for this proposed exemption. In addition, the ANPRM asked whether certain flexible consent requirements could be imposed on some of these studies that would permit the use of a broad consent for future use, with a requirement that a subject's specific consent would be required before their biospecimens could be used for special categories of research.

Many of the comments supported the discussion in the ANPRM of eliminating the requirement that the information or biospecimens be "existing" at the time the study was suggested for exemption. However, a majority strongly disagreed that biospecimens should be considered or treated as though they were inherently identifiable. A majority also opposed the suggestion that there be consent requirements for the research use of nonidentifiable biospecimens collected for purposes other than the current research study.

Some commenters also favored requiring IRB review and approval for the use of identifiable private information and identifiable biospecimens, rather than permitting the use of a broad consent for future use to satisfy the regulatory requirement for consent. These commenters indicated that IRB review of specific research studies, and the IRB's consideration of whether a study specific informed consent should be required or whether informed consent could be waived, was more protective of human subjects than the ANPRM recommendation of permitting use of a broad consent for future use.

The ANPRM asked several questions about the interpretation and applicability of current exemption category 5 (current Rule at §__.101(b)(5)), including the scope of the current

interpretation of the category 5 exemption. The ANPRM also asked if the current category 5 guidance entitled, "OPRR Guidance on 45 CFR 46.101(b)(5)"[104] should be revised, or if additional guidance on the interpretation of exemption category 5 is needed.

There were few responses to these questions. However, those that did comment noted that this category is often misunderstood by IRBs and, at best, would benefit from clearer guidance. Commenters said that examples would help investigators and IRBs understand when research activities included in demonstration projects constitute human subjects research subject to the Common Rule. Commenters noted that many activities in demonstration projects do not contribute to generalizable knowledge as they produce results that are relevant only to the program being assessed; as such, many of these activities do not meet the Common Rule's regulatory definition of "research" and thus fall outside of the rule. Other commenters said that some activities in this category are mandated or required by law or regulation and should not be considered to be under the purview of the Common Rule. It was noted that the critical issue in these studies should be protecting privacy and as long as measures are in place to do so, additional protections are not required.

3. Expedited Review

The ANPRM discussed and sought comment on three possible changes to the review of research through expedited review: (1) revising the definition of minimal risk, which is one of the criteria for determining whether a study is eligible for expedited review; (2) changing the default

[104] See 48 FR 9266-9270 (Mar 4, 1983).(OPRR Guidance on 45 CFR 46.101(b)(5), Exemption for Research and Demonstration Projects on Public Benefit and Service Programs, http://www.hhs.gov/ohrp/policy/exmpt-pb.html)

position so that research on the expedited review list could generally be presumed to involve minimal risk; (3) revising the criteria for approval of research studies under expedited review; and (4) allowing appropriately trained individuals who are not IRB members to conduct expedited reviews.

Definition of Minimal Risk: The ANPRM asked for public comment on whether the current regulatory definition of minimal risk[105] was appropriate. The definition of minimal risk has relevance to determining whether a protocol is eligible for expedited review. Public comments expressed both a desire to retain the current definition (slightly less than half) and a desire for changing it (slightly more than half). There were few common themes in the suggested changes to the language other than seeking clarification on what baselines an IRB should consider in determining the meaning of "daily life" and "routine physical or psychological examinations." Several commenters acknowledged the difficulty of arriving at a concise definition for all circumstances. Those opposed to changing the definition said that IRBs generally understand how to interpret the language and that difficult or challenging application of the definition will persist regardless of the definition for those areas of research where risks are difficult to assess. Commenters recognized that the risks encountered in daily life can vary greatly depending on many factors, for example, where people live, what kind of work they are involved in, what their social and economic environment is, and their baseline health status. Thus, IRBs need to consider all of these issues in making a determination about the level of risk.

[105] The current rule states that minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (45 CFR 46.102(i))

Eligibility for Expedited Review: The ANPRM suggested updating the current list of research activities eligible for expedited review; this list was last updated in 1998. It also considered mandating that a federal panel periodically (such as every year or every two years) review and update the list, based on a systematic, empirical assessment of the levels of risk. This would provide greater clarity about what would be considered to constitute minimal risk, and create a process that allows for routinely reassessing and updating the list of research activities that would qualify as minimal risk. The ANPRM asked for public comments on categories of research that should be considered for addition to the current list.

Several commenters provided suggestions for additions to the list of research activities eligible for expedited review. Others encouraged OHRP to consider developing principles for expedited review, rather than creating a revised list of research activities. Commenters suggested a more timely and consistent review of the list because of the rapidly changing state of science and technology.

The ANPRM also discussed the potential adoption of a default presumption in the rule that a study that includes only activities on the expedited review list is a minimal risk study and should receive expedited review. A reviewer would have the option of determining that the study should be reviewed by a convened IRB when that conclusion is supported by the specific circumstances of the study. The ANPRM also asked for comments on whether IRBs should be required to report instances when they overrode the default presumption that research appearing on the posted list did not warrant review by a convened IRB.

Commenters overwhelmingly welcomed the clarification that categories of research found on the published list should be presumed to be minimal risk. However, commenters were largely opposed to requiring IRBs to report instances when they conducted a review by the convened membership (versus an expedited review) for studies appearing on the list. They were opposed because of the additional administrative burden and also because they felt such a requirement would undermine the purview of local review and open IRBs up to second-guessing by OHRP.

Criteria for Approval under Expedited Review: The ANPRM asked whether all of the §__.111 criteria should still be required for approval of studies that qualify for expedited review, and if not, which ones should not be required. Currently, before an IRB may approve a research study, including research that is being reviewed under an expedited procedure, the IRB must find that the criteria at §___.111 have been met.

With regard to revising the criteria used for expedited review, comments were mixed. Nearly half of those commenting expressed concerns about establishing two sets of ethical standards for IRB review—one for convened review and one for expedited review. They asserted ethical and administrative concerns about operating under two sets of conditions and principles—that is, expedited review should not be viewed as less stringent than review conducted by a convened IRB.

Those commenters in favor of retaining the current criteria wrote that a double standard could result in arbitrary IRB decision making. In addition, many wrote that the current criteria are well understood by IRB members and the tendency to review a protocol through a convened IRB

when expedited review would be permissible is more a function of institutional concerns about liability than the regulatory requirements. They cited the regulatory language at §__.111, which frequently contains the phrase "wgeb appropriate," so that the reviewer(s) can exercise discretion in whether all of the criteria need to be applied.

Those in favor of revising the elements most often cited the irrelevance of some of the criteria for minimal risk research, such as the need to ensure that risks to subjects are reasonable in relation to anticipated benefits (§__.111)(a)(2)). They stated that in the case of minimal risk research, the need to balance risks with benefits is not pertinent. Some commenters asked OHRP to develop guidance for the expedited reviewer in interpreting the most relevant criteria during expedited review.

Several commenters noted that if the revised regulations remove the requirement for continuing review of studies initially reviewed through expedited review it would alleviate administrative burden; thus more extreme measures such as revising the review criteria would be less compelling.

Who May Conduct Expedited Reviews: The ANPRM asked for public comment on the advantages and disadvantages of requiring that expedited review be conducted by an IRB member versus an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB.

With regard to allowing a non-IRB member to conduct expedited review, comments were divided nearly evenly between those who opposed such a change and those who supported it. Those who opposed it cited the need for continuity and consistency across IRBs, as well as expressing concerns about accountability and liability. Those in favor of such a revision cited the expertise of IRB staff members and their ability to review many expedited studies at the same level as a member of the IRB.

4. Streamlining IRB Review

Cooperative Research: The ANPRM sought public comment on the feasibility, advantages, and disadvantages of mandating that all domestic (U.S.) sites in a study involving more than one institution rely on a single IRB for that study. This would apply regardless of whether the study underwent convened review or expedited review. Further, it would only affect which IRB would be designated as the reviewing IRB for institutional compliance with the IRB review requirements of the Common Rule. It would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal ethics reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule.

To address institutions' concerns about OHRP's practice of enforcing compliance with the Common Rule through the institutions that are engaged in human subjects research, the ANRPM also suggested that appropriate accompanying changes could be made in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory

requirements.[106] This change was discussed only for U.S. sites in multi-institutional studies. The ANPRM suggested that, in most cases, independent local IRB reviews of international sites are appropriate because it might be difficult for an IRB in the U.S. to adequately evaluate local conditions in a foreign country that could play an important role in the ethical evaluation of the study.

This issue attracted a large number of comments, and revealed nearly evenly divided perspectives. Researchers and disease advocacy groups tended to favor the single IRB review requirement. IRB and institutional representatives tended to be opposed to the possible requirement, though many indicated single IRB review should be encouraged. Support was especially strong for single IRB review for cooperative clinical trials for which the evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent form and process generally do not require the unique perspective of a local IRB. Moreover, depending on the nature of the study, FDA may not permit differences in protocols across sites, which further bolstered commenters' views that the requirements be harmonized across the Common Rule and FDA requirements. Commenters reported incidences of IRBs continuously second-guessing each other, which delayed studies to the point that subject recruitment opportunities were foregone or lost. This problem seemed especially critical in studies of rare diseases and cancers, which nearly always involve multiple research sites.

Support for the use of a single IRB, however, was not restricted to clinical trials. Several commenters cited long delays and burdensome requirements resulting from multiple reviews of

[106] 74 FR 9578 (Mar. 5, 2009). Also available at http://www.hhs.gov/ohrp/newsroom/rfc/com030509.html.

studies in the behavioral and social sciences. In addition to the view that these administrative requirements do not enhance protections, supporters of a single IRB review of cooperative studies cited the frequent need for maintaining consistency across sites, which can be degraded by multiple reviews.

Despite support for the ANPRM suggestion, several commenters expressed concern about making such a provision mandatory, stating that the current regulations at §__.114 currently permit the use of joint review arrangements for cooperative research. They noted that although this option exists, institutions might be hesitant to use it because of liability concerns and the unwillingness of institutions or IRBs to rely on the judgment of other institutions or IRBs. However, several commenters expressed concern about signaling the acceptability of a single IRB for review while allowing institutions to continue to conduct their own ethics review, fearing that such a policy would not correct the current situation, which tends to favor multiple reviews. Thus, they commented that mandating a single IRB might be the only way to achieve the goals of streamlining review while ensuring protections.

Another issue raised was the need to set clearer expectations of the responsibilities of local IRBs that are not designated as the central IRB. A number of commenters supporting the requirement for a central IRB also requested that OHRP issue guidance on how to select the IRB, responsibilities of all parties, and clarifying compliance and enforcement policies. Several commenters also requested that OHRP develop a template for reliance agreements to replace inter-institutional agreements currently in use.

Those who expressed concern about the use of a single IRB said some studies, especially in the behavioral and social sciences, might involve significant contextual issues reflecting community norms, standards, and practices, or local culture and customs. Use of a distant IRB might not consider and best protect subjects based on community norms. Others noted that such concerns can be addressed by investigators or IRBs submitting "points to consider" regarding significant contextual or cultural considerations of relevance to their site.

A primary issue posed by those opposed to mandating use of a single IRB in cooperative studies focused on potential loss of accountability and increased liability for the institutions where the research is conducted but where the reviewing IRB is not located.

Streamlining Documentation Requirements for Expedited Studies: Under the current Common Rule, investigators typically must submit the same documents including a detailed protocol, informed consent forms, and any other supporting documents, regardless of whether the study will be reviewed by a convened IRB or be approved by the expedited review process. The ANPRM suggested that although it is important to document why research qualifies for expedited review, it is unclear whether the time and effort expended in such preparation activities result in increased benefit in terms of protecting subjects.

The ANPRM further suggested that standard templates for protocols and consent forms and sample versions of those documents that are specifically designed for use in the most common types of studies might facilitate expedited review. Such forms would need to be carefully designed to eliminate those elements that are of relevance only in studies that pose greater than

minimal risks and to substantially reduce the current burden of researchers involved in producing these documents and of the IRB members who review them. The ANPRM asked whether there were specific changes that could be made to reduce the burden imposed on investigators and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects.

There were few comments on streamlining the document submission requirements for expedited review, and there was no consensus among those who did comment about how to achieve that goal.

Continuing Review: The ANPRM asked for public comments on eliminating continuing review for all minimal risk studies that undergo expedited review, unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects.

Additionally, the ANPRM suggested that, for studies initially reviewed by a convened IRB, continuing review would not be required after the study reaches the stage where procedures are limited to either: (1) analyzing data (even if it is identifiable), or (2) accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition or disease (such as periodic CT scans to monitor whether the subjects' cancers have recurred or progressed) unless specifically mandated by the IRB,. This would be a change from the current Rules, which require at least expedited IRB review of the activities described in (1) and (2) above. The requirement that research involving greater than minimal risk be reviewed by a convened IRB would not be changed from the current system.

By eliminating the requirement for continuing review of these activities, the ANPRM suggested that this change would allow for more effective use of IRBs' time by enabling the IRB to focus on reviewing information that is necessary to ensure protection of research subjects. Requiring annual continuing review of research studies involving only activities that are already well-documented to generally involve no more than minimal risk may provide little if any added protection to subjects, and it may be preferable for IRB resources to be devoted to research that poses greater than minimal risk.

The ANPRM asked for public comment on whether it would be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the default policy of no continuing review required for the situations described above. The information, if collected by OHRP, might be useful in developing future guidance or revising the categories of research eligible for expedited review.

A large majority of public comments were in favor of the suggested revisions. Many were comfortable with continuing to allow IRBs or reviewers the discretion to require continuing review in certain circumstances, citing the historical position of OHRP in considering the regulations as the floor, rather than the ceiling, for protecting the subjects of research. Those who were opposed to the revisions cited concerns about institutional liability, the possibility for increased noncompliance among investigators no longer required to "check in," and possible breakdowns in lines of communications between investigators and IRBs. Others expressed

concerns about how an IRB will know that a study has ended and suggested that investigators be required to file a notice of closure of a study.

Note that the November 10, 2010, document entitled, "Guidance on IRB Continuing Review of Research" states:

> OHRP is aware that many IRBs require investigators to submit final closeout reports when a research study is completed or no longer involves human subjects. Since the HHS regulations at 45 CFR part 46 do not require submission of such reports, institutions are free to decide whether and when such reports are required and what their content should include. [107]

Commenters overwhelmingly opposed requiring IRBs to periodically report on the instances when they (or a reviewer) elect to override the default position of no continuing review required. The reasons for opposition included: (1) additional administrative burden that would negate the reduced burden gained; (2) the possibility that requiring such reporting would discourage IRBs/reviewers from making an override decision; and (3) concerns that such reports would lead to OHRP second-guessing IRB decisions and imposing compliance oversight in an extra-regulatory decision. Several commenters suggested that OHRP could use other means than this requirement for developing guidance and improving educational efforts regarding expedited and continuing review.

[107] Office for Human Research Protections. (2010, November 10). Identifying the Point When Continuing Review is no Longer Necessary. Retrieved from Guidance on IRB Continuing Review of Research: http://www.hhs.gov/ohrp/policy/continuingreview2010.html#section-k

5. Improving Harmonization

The ANPRM did not suggest any specific approaches to harmonization but asked for public comment on a set of questions focused on: (1) the extent to which differences in guidance on research protections from different agencies strengthen or weaken protections for human subjects; (2) the extent to which differences in guidance on research protections from different agencies facilitate or inhibit the conduct of research domestically and internationally; and (3) the desirability of all Common Rule agencies issuing one set of guidance.

Responses to questions about the need for harmonization across Common Rule agencies reflected widespread support for such efforts. Several commenters acknowledged the difficulty of getting all Common Rule agencies to agree on all issues, as each has a different mission and research portfolio. However, they encouraged seeking harmonized guidance whenever possible.

Regulatory Text

For the reasons set forth in the preamble, it is proposed that the Federal Policy for the Protection of Human Subjects be amended as follows:

PART __ PROTECTION OF HUMAN SUBJECTS

__.101 To what does this policy apply?

__.102 Definitions for purposes of this policy.

__.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.

__.104 Exempt research.

__.105 Protection of biospecimens and identifiable private information.

__.106 [Reserved]

__.107 IRB membership.

__.108 IRB functions and operations.

__.109 IRB review of research.

__.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

__.111 Criteria for IRB approval of research.

__.112 Review by institution.

__.113 Suspension or termination of IRB approval of research.

__.114 Cooperative research.

__.115 IRB records.

__.116 General requirements for informed consent.

__.117 Documentation of informed consent.

__.118 Applications and proposals lacking definite plans for involvement of human subjects.

__.119 Research undertaken without the intention of involving human subjects.

__.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.

__.121 [Reserved]

__.122 Use of Federal funds.

__.123 Early termination of research support: Evaluation of applications and proposals.

__.124 Conditions.

§__.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, and as detailed in §__.104, this policy applies to the research described in paragraphs (a)(1) and (2) of this section. The entities that must comply with this policy are institutions that are engaged in research described in paragraphs (a)(1) or (2) of this section, and institutional review boards (IRBs) reviewing research that is subject to this policy.

(1) All research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal

civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.

(2) All clinical trials as defined by this policy, irrespective of funding source, that meet all of the following conditions:

(i) The clinical trials are conducted by an institution that receives support from a Federal department or agency for human subjects research that is not excluded from this policy under §__.101(b)(2) and does not qualify for exemption in accordance with §__.104;

(ii) The clinical trials are not subject to regulation by the Food and Drug Administration; and

(iii) The clinical trials are conducted at an institution located within the United States.[1]

(b) The following categories of activities are excluded from this policy, and no procedural, recordkeeping, or other requirements of this policy apply to the activities other than the conditions specified for the relevant category or categories:

(1) The following activities are excluded because they are *deemed not to be research*, as defined in §__.102(l), for the purposes of this regulation:

[1] Under this provision, only 45 CFR part 46, subpart A, applies to all clinical trials meeting the applicable conditions. This provision does not require clinical trials to comply with the requirements of 45 CFR part 46, subparts B, C, and D.

(i) Data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purpose other than the currently proposed activity, or is obtained through oral or written communications with individuals (e.g., surveys or interviews).

(ii) Oral history, journalism, biography, and historical scholarship activities that focus directly on the specific individuals about whom the information is collected.

(iii) Collection and analysis of data, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(iv) Quality assurance or improvement activities involving the implementation of an accepted practice to improve the delivery or quality of care or services (including, but not limited to, education, training, and changing procedures related to care or services) if the purposes are limited to altering the utilization of the accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. This exclusion does not cover the evaluation of an accepted practice itself.

(v) Public health surveillance activities, including the collection and testing of biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority and limited to those necessary to allow the public health authority to

identify, monitor, assess, or investigate potential public health signals or the onset of a disease outbreak, including trends, or signals, and patterns in diseases, or a sudden increase in injuries from using a consumer product, or conditions of public health importance, from data, and including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made disasters.

(vi) Surveys, interviews, surveillance activities and related analyses, or the collection and use of biospecimens conducted by a defense, national security, or homeland security authority solely for authorized intelligence, homeland security, defense, or other national security purposes.

(2) The following activities are excluded because they are considered to be ***low-risk*** human subjects research, when already subject to independent controls without application of these regulatory requirements. These exclusions do not apply when the research includes the collection or analysis of biospecimens. All of the following exclusion categories apply to research subject to this policy and to research subject to the additional requirements of 45 CFR part 46, subparts B, C, and D, however, the exclusion at paragraph (b)(2)(i) of this section applies only to research subject to subpart D for research involving educational tests, or observations of public behavior when the investigator does not participate in the activities being observed.

(i) Research, not including interventions, that involves the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) uninfluenced by the investigators, if at least one of the following criteria is met:

(A) The information is recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.; research information will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note; and all of the information collected, used, or generated as part of the research will be maintained in a system or systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a.

(ii) Research involving the collection or study of information that has been or will be acquired solely for non-research activities or were acquired for research studies other than the proposed research study, when either of the following two criteria is met:

(A) These sources are publicly available, or

(B) The information is recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, the investigator

does not contact the subjects, and the investigator will not re-identify subjects or otherwise conduct an analysis that could lead to creating identifiable private information.

(iii) Research conducted by a Federal department or agency using government-generated or government-collected information obtained for non-research purposes (including criminal history data), if the information originally involved a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.; the information is maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note; and all of the information collected, used, or generated as part of the research is maintained in a system or systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a.

(iv) Research as defined by this policy that involves only data collection and analysis involving the recipient's use of identifiable health information when such use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for the purpose of "public health activities" as described under 45 CFR 164.512(b).

(3) The following activities are excluded because they are considered to be *low-risk* human subjects research activities that *do not meaningfully diminish subject autonomy*. The following exclusion category applies to research subject to this policy and to research subject to the additional requirements of 45 CFR part 46, subparts B, C, or D.

(i) The secondary research use of a non-identified biospecimen that is designed only to generate information about an individual that already is known, including but not limited to the development and validation of certain tests and assays (such as research to develop a diagnostic test for a condition using specimens from individuals known to have the condition and those known not to have the condition), quality assurance and control activities, and proficiency testing.

(ii) [Reserved]

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy, which judgment shall be exercised consistent with the ethical principles of the Belmont Report.[2]

(d) Department or agency heads may require additional protections for specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Federal department or agency but not otherwise covered by this policy. Advance public notice will be required when those additional requirements apply to entities outside of the Federal department or agency itself.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations that provide additional protections for human subjects.

[2] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Apr. 18, 1979).

(f) This policy does not affect any state or local laws or regulations that may otherwise be applicable and that provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations that may otherwise be applicable and that provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the *Federal Register* or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy provided the alternative procedures to be followed are consistent with the principles of the Belmont Report.[3] Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these

[3] *Id.*

actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, or to the equivalent office within the appropriate Federal department or agency, and shall also publish them in the *Federal Register* or in such other manner as provided in department or agency procedures. The waiver notice must include a statement that identifies the conditions under which the waiver will be applied and a justification as to why the waiver is appropriate for the research, including how the decision is consistent with the principles in Belmont Report. Each Federal department or agency conducting or supporting the research must establish, on a publicly accessible federal website, a list of the research for which a waiver has been issued.

(j) Federal guidance on the requirements of this policy shall be issued only after consultation, for the purpose of harmonization (to the extent appropriate), with other Federal departments and agencies that have adopted this policy, unless such consultation is not feasible.

(k) *Transition provisions*—(1) *Research initiated prior to the compliance dates.* Ongoing human subjects research in which human subjects (as defined by this policy) were involved prior to the compliance dates for the cited provisions need not comply with the additional requirements of this subpart at §§ __.101(a)(2), __.103(e), __.104(c) through (f), __.105, __.108(a)(2), __.109(f)(2), __.111(a)(7) and (8), __.114, __.115(a)(10) and (11), __.116, and __.117 that became effective on [*effective date of the final rule*].

(2) *Use of prior collections of biospecimens*. Research involving the use of prior collections of biospecimens that meets both of the following criteria need not comply with the requirements of these regulations:

(i) The biospecimens were collected for either research or non-research purposes before the compliance date for the additional requirements of this subpart at §__.102(e)(1)(iii), and

(ii) Research use of the biospecimens occurs only after removal of any individually identifiable information associated with the biospecimens.

§__.102 Definitions for purposes of this policy.

(a) *Certification* means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

(b) *Clinical trial* means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

(c) *Department or agency head* means the head of any Federal department or agency, for example, the Secretary, HHS, and any other officer or employee of any Federal department or agency to whom the authority provided to the department or agency head by these regulations has been delegated.

(d) *Federal department or agency* refers to a Federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (e.g., HHS, the Department of Defense, or the Central Intelligence Agency).

(e)(1) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains data through intervention or interaction with the individual, and uses, studies, or analyzes the data;

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information; or

(iii) Obtains, uses, studies, or analyzes biospecimens.

(2) *Intervention* includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(3) *Interaction* includes communication or interpersonal contact between investigator and subject.

(4) *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be shared or made public (e.g., a medical record or clinically obtained biospecimen).

(5) *Identifiable private information* is private information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

(f) *Institution* means any public or private entity, or department or agency (including federal, state, and other agencies).

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(j) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The Secretary of HHS will maintain guidance that includes a list of activities considered to involve no more

than minimal risk. This list will be re-evaluated no later than every 8 years based on recommendations from the Federal departments and agencies and the public.

(k) *Public health authority* (consistent with 45 CFR 164.501) means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

(l) *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

§__.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.

(a) Each institution engaged in research that is covered by this policy, with the exception of research excluded from this policy under §__.101(b) or eligible for exemption under §__.104(d), and that is conducted or supported by a Federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements

of this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office. Federal departments and agencies will conduct or support research covered by this policy only if the institution has provided an assurance that it will comply with the requirements of this policy, as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB.

(b) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(c) The department or agency head may limit the period during which any assurance shall remain effective or otherwise condition or restrict the assurance.

(d) Certification is required when the research is supported by a Federal department or agency and not otherwise excluded under §__.101(b), waived under §__.101(i), or exempted under §__.104(d), (e), or (f)(2). Institutions shall certify that each proposal for research covered by this §__.103 has been reviewed and approved by the IRB. Such certification must be submitted as

prescribed by the Federal department or agency component supporting the research. Under no condition shall research covered by this §__.103 be initiated prior to receipt of the certification that the research has been reviewed and approved by the IRB.

(e) For non-exempt research involving human subjects covered by this policy that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall establish and follow procedures for documenting the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between the institution and the IRB, or by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution).

(Approved by the Office of Management and Budget under Control Number)

§__.104 Exempt research.

(a) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories in paragraphs (d) through (f) of this section are not subject to the requirements of this policy, other than those specified in the category.

(b) *Use of the exemption categories for research subject to the requirements of subparts B, C, and D.* Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) *Subpart B.* Each of the exemptions at this §__.104 may be applied to research conducted under subpart B if the conditions of the exemption are met.

(2) *Subpart C.* The exemptions at this §__.104 do not apply to research conducted under subpart C, except for research aimed at a broader population that consists mostly of non-prisoners but that incidentally includes some number of prisoners.

(3) *Subpart D.* Only the exemptions at paragraphs (d)(1), (2), (4), (e)(2), and (f)(1) and (2) of this section may be applied to research conducted under subpart D if the conditions of the exemption are met.

(c) Federal departments and agencies shall develop a decision tool to assist in exemption determinations. Unless otherwise required by law, exemption determinations shall be made by an individual who is knowledgeable about the exemption categories and who has access to sufficient information to make an informed and reasonable determination, or by the investigator or another individual at the institution who enters accurate information about the proposed research into the decision tool, which will provide a determination as to whether the study is exempt. If the decision tool is used, further assessment or evaluation of the exemption determination is not required. An institution or, when appropriate, the IRB, must maintain records of exemption determinations made for research subject to the requirements of this policy for which the institution or IRB exercises oversight responsibility. These records must include, at a minimum, the name of the research study, the name of the investigator, and the exemption

category applied to the research study. Maintenance of the completed decision tool shall be considered to fulfill this recordkeeping requirement.

(1) For studies exempted pursuant to paragraph (d)(2) of this section, the recordkeeping requirement will be deemed satisfied by the published list required at paragraph (d)(2)(i) of this section.

(2) [Reserved] .

(d) The following categories of exempt human subjects research generally involve a low-risk intervention with human subjects, must be recorded as required in paragraph (c) of this section, and do not require application of standards for information and biospecimen protection provided in §__.105 or informed consent. Only paragraph (d)(2) of this section allows for the collection and use of biospecimens:

(1) Research conducted in established or commonly accepted educational settings when it specifically involves normal educational practices. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods that are not likely to adversely impact students' opportunity to learn required educational content in that educational setting or the assessment of educators who provide instruction.

(2) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine public benefit or service programs,

including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible federal website or in such other manner as the department or agency head may prescribe, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to or upon commencement of the research.

(ii) [Reserved]

(3)(i) Research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses (including data entry) or video recording if the subject prospectively agrees to the intervention and data collection and at least one of the following criteria is met:

(A) The information obtained is recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects; or

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

(ii) For the purpose of this provision, benign interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the

subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. If these criteria are met, such benign interventions might include research activities in which a subject is asked to read materials, review pictures or videos, play online games, solve puzzles, or perform cognitive tasks.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception as described in paragraph (d)(3)(iv) of this section.

(iv) For the purpose of this provision, authorized deception is prospective agreement by the subject to participate in research where the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

(4) Taste and food quality evaluation and consumer acceptance studies

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(e) The following categories of exempt human subjects research allow for the collection of sensitive information about human subjects, must not involve biospecimens, must be recorded as required in paragraph (c) of this section, and require application of standards for information and biospecimen protection provided in §__.105:

(1) Research, not including interventions, involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording), if the information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects.

(2) Secondary research use of identifiable private information that has been or will be acquired for non-research purposes, if the following criteria are met:

(i) Prior notice has been given to the individuals to whom the identifiable private information pertains that such information may be used in research; and

(ii) The identifiable private information is used only for purposes of the specific research for which the investigator or recipient entity requested access to the information.

(f) The following categories of exempt human subjects research involve biospecimens or identifiable private information, must be recorded as required in paragraph (c) of this section, require application of standards for information and biospecimen protection as described in §__.105, and require informed consent and limited IRB review to the extent described in each category or otherwise required by law:

(1)(i) Storage or maintenance for secondary research use of biospecimens or identifiable private information that have been or will be acquired for research studies other than for the proposed research study, or for non-research purposes, if the following criteria are met:

(A) Written consent for the storage, maintenance, and secondary research use of the information or biospecimens is obtained in accordance with §__.116(c) and (d)(2), and the template published by the Secretary of HHS in accordance with §__.116(d)(1) must be used. Oral consent, if obtained during the original data collection and in accordance with §__.116(c) and (d)(3), would be satisfactory for the research use of identifiable private information initially acquired in accordance with activities excluded from this policy under §__.101(b)(2)(i) or exempt from this policy in accordance with §__.104(d)(3) or (4), or §__.104(e)(1);

(B) The reviewing IRB makes the determinations required by §__.111(a)(9).

(ii) [Reserved.]

(2)(i) Research involving the use of biospecimens or identifiable private information that have been stored or maintained for secondary research use, if consent for the storage, maintenance, and secondary research use of the information and biospecimens was obtained as detailed in paragraph (f)(1)(i)(A) of this section.

(ii) If the investigator anticipates that individual research results will be provided to a research subject, the research may not be exempted under this provision and must be reviewed by the IRB and informed consent for the research must be obtained to the extent required by §__.116(a) and (b).

§__.105 Protection of biospecimens and identifiable private information

(a) *In General.* Institutions and investigators conducting research that is subject to this policy, or that is exempt from this policy under §__.104(e) or (f), involving the collection, storage, or use of biospecimens or identifiable private information, shall implement and maintain reasonable and appropriate safeguards as specified in paragraph (b) of this section to protect biospecimens or identifiable private information that they collect, obtain, receive, maintain, or transmit for research. The safeguards shall reasonably protect against anticipated threats or hazards to the security or integrity of the information or biospecimens, as well as reasonably protect the information and biospecimens from any intentional or unintentional use, release, or disclosure that is in violation of paragraph (c) of this section. IRB review of the safeguards required by this section is not required, except to the extent required by §__.104(f)(1).

(b) *Safeguards requirements*. The Secretary of HHS shall establish and publish for public comment a list of specific measures that the institution or investigator may implement that will be deemed to satisfy the requirement for reasonable and appropriate safeguards. The list will be evaluated as needed, but at least every 8 years, and amended, as appropriate, after consultation with other Federal departments and agencies. The institutions and investigators identified in paragraph (a) of this section shall implement paragraph (a) of this section by choosing either to apply the safeguards identified by the Secretary as necessary to protect the security or integrity of and limit disclosure of biospecimens and electronic and non-electronic identifiable private information, or to apply safeguards that meet the standards in 45 CFR 164.308, 164.310, 164.312, and 45 CFR 164.530(c). For Federal departments and agencies that conduct research activities that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of

the information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and the research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq., these research activities automatically will be considered in compliance with the Secretary's reasonable and appropriate safeguards standards, unless or until any additional safeguards are identified by the Secretary of HHS.

(c) *Limitations on use, release, and disclosure*. Unless otherwise required by law, institutions and investigators shall use or release biospecimens or use or disclose identifiable private information collected or maintained for research only:

(1) For human subjects research regulated by this policy;

(2) For public health purposes;

(3) For any lawful purpose with the consent of the subject; or

(4) For other research purposes if the institution or investigator has obtained adequate assurances from the recipient that

(i) The recipient will implement and maintain the level of safeguards required by paragraph (b) of this section;

(ii) Except for research that qualifies for exclusion under §__.101(b) or exemption under §__.104 the releasing or disclosing institution or investigator shall obtain documentation from the recipient that the research has been approved under §__.111 to the extent required before releasing biospecimens or disclosing identifiable private information; and

(iii) The recipient shall not further release the biospecimens or disclose identifiable private information except for human subjects research regulated by this policy, or for other

purposes permitted by this paragraph. For the purposes of this requirement, an institution or investigator shall obtain adequate assurances through the use of a written agreement with the recipient that the recipient will abide by these conditions.

(d) The provisions of this section do not amend or repeal, and shall not be construed to amend or repeal, the requirements of 45 CFR parts 160 and 164 for the institutions or investigators, including Federal departments or agencies, to which these regulations are applicable pursuant to 45 CFR 160.102.

§__.106 [Reserved]

§__.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or

undue influence, such as children, prisoners, pregnant women, physically or mentally disabled persons, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

(b) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(c) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(d) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(e) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§__.108 IRB functions and operations.

(a) In order to fulfill the requirements of this policy each IRB shall:

(1) Have access to meeting space and sufficient staff to support the IRB's review and recordkeeping duties;

(2) Prepare and maintain a current list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, for example, full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant;

(3) Establish and follow written procedures for:

(i) Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(ii) Determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(4) Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of

(i) Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(ii) Any suspension or termination of IRB approval.

(b) Except when an expedited review procedure is used (as described in §__.110), an IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§__.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy that do not qualify for exemption pursuant to §__.104(d), (e), or (f)(2).

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §__.116. The IRB may require that information, in addition to that specifically

mentioned in §__.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §__.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, not less than once per year, except as described in §__.109(f).

(f)(1) Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §__.110;

(ii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(A) Data analysis, including analysis of identifiable private information, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition; or

(iii) Research reviewed by the IRB in accordance with the limited IRB review procedure described in §__.111(a)(9).

(2) The IRB must receive confirmation on an annual basis that the research is still ongoing and that no changes have been made to the research that would require the IRB to conduct continuing review of the research.

(g) An IRB shall have authority to observe or have a third party observe the consent process and the research.

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§__.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary of HHS, has established, and published as a Notice in the *Federal Register*, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the *Federal Register* for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b)(1) An IRB may use the expedited review procedure to review the following:

(i) Some or all of the research appearing on the list, unless the reviewer determines that the study involves more than minimal risk;

(ii) Minor changes in previously approved research during the period for which approval is authorized; or

(iii) Research that is being reviewed to determine whether it qualifies for exemption in accordance with §__.104(f)(1) in order to determine that the requirements of §__.111(a)(9) are satisfied.

(2) Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §__.108(b).

(c) Each IRB that uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals that have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§__.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

(i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children,

prisoners, pregnant women, physically or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §__.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by, §__.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, in addition to the requirements in §__.105, if the IRB determines that the standards for information and biospecimen protection in §__.105 are not sufficient to protect the privacy of subjects and the confidentiality of data.

(8) If the investigator proposes a research plan for returning clinically relevant results to subjects, that the plan is appropriate.

(9) For purposes of conducting the limited IRB review as required by §__.104(f)(1), the IRB need not make the determinations at paragraphs (a)(1) through (8) of this section, and shall determine that the following requirements are satisfied:

(i) The procedures for obtaining broad consent for storage, maintenance, and secondary research use of biospecimens or identifiable private information will be conducted in accordance with the requirements of the first paragraph in §__.116.

(ii) If there will be a change for research purposes in the way the biospecimens or information are stored or maintained, that the privacy and information protection standards at §__.105 are satisfied for the creation of any related storage database or repository.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, physically or mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§__.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§__.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a

statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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§__.114 Cooperative research.

(a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.

(b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be selected by the Federal department or agency supporting or conducting the research or, if there is no funding agency, by the lead institution conducting the research.

(2) The following research is not subject to the requirements of this provision:

(i) Cooperative research for which more than single IRB review is required by law; or

(ii) Research for which the Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular study.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

§__.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent forms, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities, including the rationale for conducting continuing review of research that has progressed to the point that it involves only one or both of the following:

(i) Data analysis, including analysis of identifiable private information, or

(ii) Accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §__.108(a)(2).

(6) Written procedures for the IRB in the same detail as described in §__.108(a)(3) and (4).

(7) Statements of significant new findings provided to subjects, as required by §__.116(b)(5).

(8) The rationale for requiring continuing review for research that otherwise would not require continuing review as described in §__.109(f)(1).

(9) The rationale for an expedited reviewer's determination that research appearing on the expedited review list described in §__.110(b)(1)(i) is more than minimal risk.

(10) The written agreement between an institution and an organization operating an IRB specifying the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy, as described in §__.103(e).

(11) Records relating to exemption determinations, as described in §__.104(c).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research that is conducted shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form, or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Federal department or agency at reasonable times and in a reasonable manner.

(c) The institution or IRB retaining the records shall safeguard identifiable private information contained within these records in compliance with §__.105.

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§__.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. The prospective subject or the representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. The information must be presented in sufficient

detail relating to the specific 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 representative's understanding of the reasons why one might or might not want to participate. In obtaining informed consent, the investigator must present first the information required by this section, before providing other information, if any, to the subject or the representative. Any informed consent form must include only the requirements of informed consent under this section, and appendices that include any other information provided to the subject or the representative. If an authorization required by 45 CFR parts 160 and 164 is combined with a consent form, the authorization elements required by 45 CFR 164.508 must be included in the consent form and not the appendices. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

(a) *Basic elements of informed consent.* Except as provided in paragraph (c), (e), or (f) of this section, in seeking informed consent the following information shall be provided to each subject or the representative:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) One of the following statements about any research that involves the collection of identifiable private information:

(i) A statement that identifiers might be removed from the data and the data that is not identifiable could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the representative, if this might be a possibility; or

(ii) A statement that the subject's data collected as part of the research, from which identifiers are removed, will not be used or distributed for future research studies.

(b) *Additional elements of informed consent***.** Except as provided in paragraphs (c), (e), or (f) of this section, when appropriate, one or more of the following elements of information shall also be provided to each subject or the representative:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the representative's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

(6) The approximate number of subjects involved in the study;

(7) 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;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) An option for the subject or the representative to consent, or refuse to consent, to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

(c)(1) *Elements of informed consent for broad consent to the storage, maintenance, and secondary research use of biospecimens or identifiable private information*. If the subject or the representative will be asked to provide broad consent to the storage or maintenance of biospecimens or identifiable private information, collected for either research studies other than the proposed research or non-research purposes, and the secondary research use of this stored material, the information required in paragraphs (a)(2), (3), (5), and (7) and, if applicable, (b)(7) through (9) of this section, shall be provided to each subject, with the following additional information:

(i) A general description of the types of research that may be conducted with information and biospecimens and the information that is expected to be generated from the research, the types of information or biospecimens that might be used in research, and the types of institutions that might conduct research with the biospecimens or information;

(ii) A description of the scope of the informed consent must be provided, including:

(A) A clear description of the types of biospecimens or information that were or will be collected and the period of time during which biospecimen or information collection will occur. This may include all biospecimens and information from the subject's medical record or other records existing at the institution at the time informed consent is sought; and

(B) For purposes of paragraph (c)(1)(ii)(A) of this section, the period of time during which biospecimen or information collection will occur cannot exceed 10 years from the date of consent. For research involving children as subjects, that time period cannot exceed 10 years after parental permission is obtained or until the child reaches the legal age for consent to the treatments or procedures involved in the research, whichever time

period is shorter. The time limitations described do not apply to biospecimens or information that initially will be collected for research purposes.

(iii) A description of the period of time during which an investigator can continue to conduct research using the subject's biospecimens and information described in paragraph (c)(1)(ii)(A) of this section (e.g., a certain number of years, or indefinitely);

(iv) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may withdraw consent, if feasible, for research use or distribution of the subject's information or biospecimens at any time without penalty or loss of benefits to which the subject is otherwise entitled, and information about whom to contact in order for the subject to withdraw consent. The statement must make clear that information or biospecimens that already have been distributed for research use may not be retrieved;

(v) If applicable, a statement notifying the subject or the representative that the subject or the representative will not be informed of the details of any specific research studies that might be conducted, including the purposes of the research, that will use the subject's information and biospecimens;

(vi) If applicable, a statement notifying the subject or the representative of the expectation that the subject's information and biospecimens are likely to be used by multiple investigators and institutions and shared broadly for many types of research studies in the future, and this information and the biospecimens might be identifiable when shared;

(vii)The names of the institution or set of institutions at which the subject's biospecimens or information were or will be collected, to the extent possible (in recognition that institutions might change names or cease to exist); and

(viii) If relevant, an option for an adult subject or the representative to consent, or refuse to consent, to the inclusion of the subject's data, with removal of the identifiers listed in 45 CFR 164.514(b)(2)(i)(A) through (Q), in a database that is publicly and openly accessible to anyone. This option must be prominently noted, and must include a description of risks of public access to the data.

(2) [Reserved]

(d)(1) The Secretary of HHS will establish, and publish in the *Federal Register* for public comment, templates for consent that will contain all of the required elements of informed consent under paragraph (c) of this section. IRB review of the broad secondary use informed consent form obtained in accordance with paragraph (c) of this section is required unless the consent is obtained using only this template, without any changes.

(2) If §__.104(f)(1) requires written consent, the consent for research use of biospecimens or identifiable private information must be documented by the use of a written consent form signed by the subject or the representative. The template for consent for research use established by the Secretary may serve as the written consent form. A copy shall be given to the person signing the form.

(3) If §__.104(f)(1) allows for oral consent, a subject's or the representative's oral consent for research use of identifiable private information must be documented such that the consent is associated with the subject's identifiable private information. If this requirement is met through the use of written documentation, the subject or the representative is not required to sign the documentation.

(4) If the subject or the representative declines to consent to the research use of biospecimens or identifiable private information, this must be documented appropriately.

(e)(1) Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials. An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the above requirement to obtain informed consent, provided the IRB finds and documents that:

(i) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(A) Public benefit or service programs;

(B) Procedures for obtaining benefits or services under those programs;

(C) Possible changes in or alternatives to those programs or procedures; or

(D) Possible changes in methods or levels of payment for benefits or services under those programs; and

(ii) The research could not practicably be carried out without the waiver or alteration.

(2) Additional criteria for waiver or alteration of consent for biospecimens. For research involving the use of biospecimens, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the above requirements to obtain informed consent, provided the IRB finds and documents the criteria in paragraph (e)(1) of this section, and the following additional criteria:

(i) There are compelling scientific reasons to conduct the research; and

(ii) The research could not be conducted with other biospecimens for which informed consent was obtained or could be obtained.

(3) If an individual was asked to consent to the storage or maintenance for secondary research use of biospecimens or identifiable private information in accordance with the requirements of this section at paragraph (c) of this section, and refused to consent, an IRB cannot waive consent for either the storage or maintenance for secondary research use, or for the secondary research use, of those biospecimens or information.

(f)(1) Waiver or alteration of consent. An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the above requirements to obtain informed consent, provided the IRB finds and documents that:

(i) The research involves no more than minimal risk to the subjects;

(ii) The research could not practicably be carried out without the requested waiver or alteration;

(iii) If the research involves accessing or using identifiable biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers;

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

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

(2) Additional criteria for waiver or alteration of consent for research involving biospecimens. For research involving the use of biospecimens, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the above requirements to obtain informed consent, provided the IRB finds and documents the criteria in paragraph (f)(1) of this section, and the following additional criteria:

(i) There are compelling scientific reasons for the research use of the biospecimens; and

(ii) The research could not be conducted with other biospecimens for which informed consent was obtained or could be obtained.

(3) If an individual was asked to consent to the storage or maintenance for secondary research use of biospecimens or identifiable private information, in accordance with the requirements of paragraph (c) of this section, and refused to consent, an IRB cannot waive consent for either the storage or maintenance for secondary research use, or for the secondary research use, of those biospecimens or information.

(g) An IRB may approve a research proposal in which investigators obtain, through oral or written communication or by accessing records, identifiable private information without individuals' informed consent for the purpose of screening, recruiting, or determining the eligibility of prospective human subjects of research, provided that the research proposal includes an assurance that the investigator will implement standards for protecting the information obtained, in accordance with and to the extent required by §__.105.

(h)(1) A copy of the final version of the informed consent form for each clinical trial conducted or supported by a Federal department or agency must be posted by the awardee or the Federal

department or agency component conducting the trial on a publicly available federal web site that will be established as a repository for such informed consent forms . The informed consent form must be posted in such form and manner as the department or agency head may prescribe, which will include at a minimum posting, in addition to the informed consent form, the name of the clinical trial and information about whom to contact for additional details about the clinical trial.

(2) The informed consent form must be posted on the federal website within 60 days after the trial is closed to recruitment.

(i) The informed consent requirements in this policy are not intended to preempt any applicable Federal, state, or local laws that require additional information to be disclosed in order for informed consent to be legally effective.

(j) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

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§__.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, and except for research for which consent is obtained in accordance with §__.116(c), informed consent shall be documented by the use of a

written informed consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the informed consent form.

(b) Except as provided in paragraph (c) of this section, the informed consent form may be either of the following:

(1) A written informed consent form that includes a form containing only the information required by §__.116, and appendices that include any other information. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.

(2) A short form written informed consent form stating that the elements of informed consent required by §__.116 have been presented orally to the subject or the subject's legally authorized representative, and that the information required by §__.116 was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c)(1) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

(i) That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

(iii) If the subjects are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. Documentation must include a description as to why signing forms is not the norm for the distinct cultural group or community.

(2) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(3) This waiver does not apply to research for which consent is required to be documented in accordance with §__.116(d)(2), (3), or (4).

(4) Documentation of informed consent may not be waived under paragraphs (c)(1)(i) or (iii) of this section for research subject to regulation by the Food and Drug Administration unless otherwise authorized by 21 CFR 56.109(c)(1).

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§__.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to Federal departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. Except for research excluded under §__.101(b), waived under §__.101(i), or exempted under §__.104(d), (e), or (f)(2), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Federal department or agency component supporting the research.

§__.119 Research undertaken without the intention of involving human subjects.

Except for research excluded under §__.101(b), waived under §__.101(i), or exempted under §__.104(d), (e), or (f)(2), in the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted by the institution to the Federal department or agency component supporting the

research, and final approval given to the proposed change by the Federal department or agency component.

§__.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the Federal department or agency through such officers and employees of the Federal department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§__.121 [Reserved]

§__.122 Use of Federal funds.

Federal funds administered by a Federal department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§__.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that Federal department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§__.124 Conditions.

With respect to any research project or any class of research projects the department or agency head of either the conducting or the supporting Federal department or agency may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

DEPARTMENT OF HOMELAND SECURITY

6 CFR Part 46

List of Subjects in 6 CFR Part 46

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Homeland Security proposes to add 6 CFR part 46, as set forth at the end of the common preamble of this document.

PART 46--PROTECTION OF HUMAN SUBJECTS

Sec.

46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

Authority: 5 U.S.C. 301; P.L. 107-296, sec. 102, 306(c); P.L. 108-458, sec. 8306.

Reginald Brothers

Under Secretary for Science and Technology, DHS

DEPARTMENT OF AGRICULTURE

7 CFR Part 1c

List of Subjects in 7 CFR Part 1c

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Agriculture proposes to revise 7 CFR part 1c, as set forth at the end of the common preamble of this document.

PART 1c--PROTECTION OF HUMAN SUBJECTS

Sec.

1c.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
1c.121 [Reserved]
1c.122 Use of Federal funds.
1c.123 Early termination of research support: Evaluation of applications and proposals.
1c.124 Conditions.

Authority: 5 U.S.C. 301.

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Catherine Woteki

Under Secretary for Research, Education, and Economics, USDA

DEPARTMENT OF ENERGY

10 CFR Part 745

List of Subjects in 10 CFR Part 745

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Energy proposes to revise 10 CFR part 745, as set forth at the end of the common preamble of this document.

PART 745--PROTECTION OF HUMAN SUBJECTS

Sec.

745.101 To what does this policy apply?
745.102 Definitions for purposes of this policy.
745.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
745.104 Exempt research.

745.105 Protection of biospecimens and identifiable private information.
745.106 [Reserved]
745 .107 IRB membership.
745.108 IRB functions and operations.
745.109 IRB review of research.
745.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
745.111 Criteria for IRB approval of research.
745.112 Review by institution.
745.113 Suspension or termination of IRB approval of research.
745114 Cooperative research.
745.115 IRB records.
745.116 General requirements for informed consent.
745.117 Documentation of informed consent.
745.118 Applications and proposals lacking definite plans for involvement of human subjects.
745.119 Research undertaken without the intention of involving human subjects.
745.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
745.121 [Reserved]
745.122 Use of Federal funds.
745.123 Early termination of research support: Evaluation of applications and proposals.
745.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 7254.

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Elizabeth Sherwood-Randall

Deputy Secretary of Energy

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

14 CFR Part 1230

List of Subjects in 14 CFR Part 1230

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the National Aeronautics and Space Administration proposes to revise 14 CFR part 1230, as set forth at the end of the common preamble of this document.

PART 1230--PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301.

Richard S. Williams

Chief Health and Medical Officer

DEPARTMENT OF COMMERCE

15 CFR Part 27

List of Subjects in 15 CFR Part 27

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Commerce proposes to revise 15 CFR part 27, as set forth at the end of the common preamble of this document.

PART 27--PROTECTION OF HUMAN SUBJECTS

Sec.

27.117 Documentation of informed consent.
27.118 Applications and proposals lacking definite plans for involvement of human subjects.
27.119 Research undertaken without the intention of involving human subjects.
27.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
27.121 [Reserved]
27.122 Use of Federal funds.
27.123 Early termination of research support: Evaluation of applications and proposals.
27.124 Conditions.

Authority: 5 U.S.C. 301.

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James Hock

Chief of Staff, Department of Commerce

SOCIAL SECURITY ADMINISTRATION

20 CFR Part 431

List of Subjects in 20 CFR Part 431

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Social Security Administration proposes to add 20 CFR part 431, as set forth at the end of the common preamble of this document.

PART 431 --PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

Carolyn W. Colvin

Acting Commissioner of Social Security

AGENCY FOR INTERNATIONAL DEVELOPMENT

22 CFR Part 225

List of Subjects in 22 CFR Part 225

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Agency for International Development proposes to revise 22 CFR part 225, as set forth at the end of the common preamble of this document.

PART 225--PROTECTION OF HUMAN SUBJECTS

Sec.

225.124 Conditions.

Authority: 5 U.S.C. 301.

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Wade Warren

Senior Deputy Assistant Administrator for Global Health

U.S. Agency for International Development

DEPARTMENT OF JUSTICE

28 CFR Part 46

AG Order No. 3553-2015

List of Subjects in 28 CFR Part 46

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Justice proposes to revise 28 CFR part 46, as set forth at the end of the common preamble of this document.

PART 46—PROTECTION OF HUMAN SUBJECTS

Sec.

46.104 Exempt research.
46.105 Protection of biospecimens and identifiable private information.
46.106 [Reserved]
46.107 IRB membership.
46.108 IRB functions and operations.
46.109 IRB review of research.
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
46.111 Criteria for IRB approval of research.
46.112 Review by institution.
46.113 Suspension or termination of IRB approval of research.
46.114 Cooperative research.
46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

Authority: 5 U.S.C. 301; 28 U.S.C. 509-510.

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Sally Quillian Yates

Deputy Attorney General

DEPARTMENT OF LABOR

29 CFR Part 21

List of Subjects in 29 CFR Part 21

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Social Security Administration proposes to add 29 CFR part 21, as set forth at the end of the common preamble of this document.

PART 21--PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 29 U.S.C. 551.

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Christopher P. Lu

Deputy Secretary of Labor

DEPARTMENT OF DEFENSE

32 CFR Part 219

List of Subjects in 32 CFR Part 219

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Defense proposes to revise 32 CFR part 219, as set forth at the end of the common preamble of this document.

PART 219--PROTECTION OF HUMAN SUBJECTS

Sec.

219.113 Suspension or termination of IRB approval of research.
219.114 Cooperative research.
219.115 IRB records.
219.116 General requirements for informed consent.
219.117 Documentation of informed consent.
219.118 Applications and proposals lacking definite plans for involvement of human subjects.
219.119 Research undertaken without the intention of involving human subjects.
219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
219.121 [Reserved]
219.122 Use of Federal funds.
219.123 Early termination of research support: Evaluation of applications and proposals.
219.124 Conditions.

Authority: 5 U.S.C. 301.

Patricia L. Toppings

OSD Federal Register Liaison

Officer, Department of Defense

DEPARTMENT OF EDUCATION

34 CFR Part 97

List of Subjects in 34 CFR Part 97

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Education proposes to amend 34 CFR part 97 as follows:

PART 97--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for part 97 continues to read as follows:

Authority: 5 U.S.C. 301; 20 U.S.C. 1221e-3, 3474.

2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Federal Policy for the Protection of Human Subjects (Basic ED Policy for Protection of Human Research Subjects)

Sec.

Arne Duncan

Secretary of Education

DEPARTMENT OF VETERANS AFFAIRS

38 CFR Part 16

List of Subjects in 38 CFR Part 16

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Veterans Affairs proposes to revise 38 CFR part 16, as set forth at the end of the common preamble of this document.

PART 16 --PROTECTION OF HUMAN SUBJECTS

Sec.

16.117 Documentation of informed consent.
16.118 Applications and proposals lacking definite plans for involvement of human subjects.
16.119 Research undertaken without the intention of involving human subjects.
16.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
16.121 [Reserved]
16.122 Use of Federal funds.
16.123 Early termination of research support: Evaluation of applications and proposals.
16.124 Conditions.

Authority: 5 U.S.C. 301; 38 U.S.C. 501, 7331, 7334.

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Robert L. Nabors II

Chief of Staff

US Department of Veterans Affairs

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

List of Subjects in 40 CFR Part 26

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 26 as follows:

PART 26 --PROTECTION OF HUMAN SUBJECTS

1. The authority citation for part 26 continues to read as follows:

Authority: 5 U.S.C. 301; 7 U.S.C. 136a(a) and 136w(a)(1); 21 U.S.C. 346a(e)(1)(C); sec. 201, Pub. L. 109-54, 119 Stat. 531.

2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Basic EPA Policy for Protection of Subjects in Human Research Conducted or Supported by EPA

Sec.

A. Stanley Meiburg,

Acting Deputy Administrator

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

List of Subjects in 45 CFR Part 46

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Health and Human Services proposes to amend 45 CFR part 46 as follows:

PART 46--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for part 46 is revised to read as follows:

Authority: 5 U.S.C. 301; 42 U.S.C. 289.

2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Sec.

46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

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Sylvia M. Burwell

Secretary, HHS

NATIONAL SCIENCE FOUNDATION

45 CFR Part 690

List of Subjects in 45 CFR Part 690

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the National Science Foundation proposes to revise 45 CFR part 690, as set forth at the end of the common preamble of this document.

PART 690--PROTECTION OF HUMAN SUBJECTS

Sec.

690.101 To what does this policy apply?
690.102 Definitions for purposes of this policy.

690.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
690.104 Exempt research.
690.105 Protection of biospecimens and identifiable private information.
690.106 [Reserved]
690.107 IRB membership.
690.108 IRB functions and operations.
690.109 IRB review of research.
690.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
690.111 Criteria for IRB approval of research.
690.112 Review by institution.
690.113 Suspension or termination of IRB approval of research.
690.114 Cooperative research.
690.115 IRB records.
690.116 General requirements for informed consent.
690.117 Documentation of informed consent.
690.118 Applications and proposals lacking definite plans for involvement of human subjects.
690.119 Research undertaken without the intention of involving human subjects.
690.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
690.121 [Reserved]
690.122 Use of Federal funds.
690.123 Early termination of research support: Evaluation of applications and proposals.
690.124 Conditions.

Authority: 5 U.S.C. 301.

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Lawrence Rudolph

General Counsel

DEPARTMENT OF TRANSPORTATION

49 CFR Part 11

List of Subjects in 49 CFR Part 11

Human research subjects, Reporting and record-keeping requirements, Research.

For the reasons stated in the preamble, the Department of Transportation proposes to revise 49 CFR part 11, as set forth at the end of the common preamble of this document.

PART 11--PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301.

Anthony R. Foxx

Secretary of Transportation

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