

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

45 CFR Parts 46, 160, and 164

Food and Drug Administration

21 CFR Parts 50 and 56

Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

AGENCIES: The Office of the Secretary, HHS, and the Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Office of the Secretary of the Department of Health and Human Services (HHS) in coordination with the Office of Science and Technology Policy (OSTP) is issuing this advance notice of proposed 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. This ANPRM seeks 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.

The current regulations governing human subjects research were developed years ago when research was predominantly conducted at universities, colleges, and medical institutions, and each study generally took place at only a single site. Although the regulations have been amended over the years, they have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics. Revisions to the current human subjects regulations are being considered because OSTP and HHS believe these changes would strengthen protections for research subjects.

DATES: To be assured consideration, comments must be received at one of the addresses provided below, no later than 5 p.m. on September 26, 2011.

ADDRESSES: You may submit comments, identified by docket ID number HHS–

OPHS–2011–0005, 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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I. Background

U.S. Federal regulations governing the protection of human subjects in research have been in existence for more than three decades. Twenty years have passed since the “Common Rule,” (codified at Subpart A of 45 CFR part 46) was adopted by 15 U.S. Federal departments and agencies in an effort to promote uniformity, understanding, and compliance with human subject protections.¹

Existing regulations governing the protection of human subjects in Food and Drug Administration (FDA)-regulated research (21 CFR parts 50, 56, 312, and 812) are separate from the Common Rule but include similar requirements.

The history of contemporary human subjects protections began in 1947 with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the

Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects.

Similar recommendations were made by the World Medical Association in its Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted in 1964 and subsequently revised many times.

Basic regulations governing the protection of human subjects in research supported or conducted by HHS (then the Department of Health, Education and Welfare) were first published in 1974. In the United States, a series of highly publicized abuses in research led to the enactment of the 1974 National Research Act (Pub. L. 93–348), which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). One of the charges to the National Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines to assure that such research is conducted in accordance with those principles. In 1979, the National Commission published “Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” also known as the Belmont Report (<http://www.hhs.gov/ohrp/policy/belmont.html>) which identified three fundamental ethical principles for all human subjects research—respect for persons, beneficence, and justice.

Based on the Belmont Report and other work of the National Commission, HHS revised and expanded its regulations for the protection of human subjects in the late 1970s and early 1980s. The HHS regulations are codified at 45 CFR part 46, subparts A through E. The statutory authority for the HHS regulations derives from 5 U.S.C. 301; 42 U.S.C. 300v–1(b); and 42 U.S.C. 289.

In 1991, 14 other Federal departments and agencies joined HHS in adopting a uniform set of rules for the protection of human subjects, the “Common Rule,” identical to subpart A of 45 CFR part 46 of the HHS regulations.

The Common Rule requires that Federally funded investigators in most instances obtain and document the informed consent of research subjects, and describes requirements for institutional review board (IRB) membership, function, operations, research review, and recordkeeping. The regulations also delineate criteria for, and levels of, IRB review. Currently, except for human subjects research that

is determined to be exempt from the regulations, Federally funded research involving human subjects is reviewed by an IRB in one of two ways: (1) By a convened IRB, or (2) through an expedited review process.

Since the Common Rule was developed, the landscape of research activities has changed dramatically, accompanied by a marked increase in the volume of research. It is estimated that total spending on health-related research and development by the drug industry and the Federal government has tripled since 1990.² While traditional biomedical research conducted in academic medical centers continues to flourish, many studies are now also conducted at community hospitals, outpatient clinics, or physician-based practices. Clinical research is regularly conducted at multiple institutions across the U.S. and other countries. Recruitment firms, bioinformatics specialists, clinical trial coordinating centers, protocol developers, data analysts, contract research organizations (CROs), data and safety monitoring committees, community-based organizations, and other entities have joined investigators and sponsors as part of the clinical research enterprise.

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 studies. The application of technologies such as functional magnetic resonance imaging in neuroscience has led to substantial advances in the understanding of human physiology, cognition, and behavior. The advent of sophisticated computer software programs, the Internet, and mobile technology have created new areas of research activity, particularly within the social and behavioral sciences, exponentially increasing the amount of information available to researchers, while providing the means to access and analyze that information. In many areas of society, researchers are being called upon to provide evidence to more effectively guide social policy and practices.

The rapid growth and expansion of human subjects research has led to many questions about whether the current regulatory framework is adequate and appropriate for the protection of human subjects in the 21st century. Furthermore, decades of experience have revealed a great deal about the functioning—and limitations—of existing regulations, and prompted critical evaluations by the

Institute of Medicine (IOM),^{3 4} the U.S. Government Accountability Office,^{5 6 7} and many scholars.^{8 9 10} Federal consideration of such revisions to the regulatory schema, in addition to the issues that suggest a need for revision, is not without precedent. In its 2001 concluding report, the National Bioethics Advisory Commission (NBAC) made 30 recommendations that addressed areas including the scope and structure of the oversight system, the level of review applied to research, emphasizing the informed consent process, documentation and waiver of informed consent, protecting privacy and confidentiality, adverse event reporting, and review of cooperative or multi-site research studies.¹¹ NBAC's recommendations are one source for the revisions in the Common Rule currently being considered. Addressing these considerations now is timely and consistent with the President's Executive Order requiring Federal agencies to review existing significant regulations to determine whether they should be modified, streamlined, expanded, or repealed to make the agency's regulatory program more effective or less burdensome in achieving the regulatory objective.¹²

The concerns about the current Common Rule can roughly be categorized into seven areas. First, the system has been criticized as not adequately calibrating the review process to the risk of research. Critics have raised concerns that some IRBs spend considerable time reviewing minimal risk research, and that some IRBs have a tendency to overestimate the magnitude and probability of reasonably foreseeable risks.¹³ Because significantly more research studies require convened IRB review, this greater IRB workload diverts time and resources from review of research that poses greater risks, theoretically resulting in inadequate attention to research that could seriously harm subjects.¹⁴

Questions have been raised about the appropriateness of the review process for social and behavioral research.^{15 16 17 18} The nature of the possible risks to subjects is often significantly different in many social and behavioral research studies as compared to biomedical research, and critics contend that the difference is not adequately reflected in the current rules. While physical risks generally are the greatest concern in biomedical research, social and behavioral studies rarely pose physical risk but may pose psychological or informational risks. 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 over-regulates such research.^{19 20 21} Further, many critics see little evidence that most IRB review of social and behavioral research effectively does much to protect research subjects from psychological or informational risks.²² Over-regulating social and behavioral research in general may serve to distract attention from attempts to identify those social and behavioral research studies that do pose threats to the welfare of subjects and thus do merit significant oversight.

Second, critics have commented about the inefficiencies of review by multiple IRBs for multi-site studies, which add bureaucratic complexity to the review process and delay initiation of research projects without evidence that multiple reviews provide additional protections to subjects.²³ There also has been a concern that the current multiple review system might actually be leading to weaker protections for subjects than if there were fewer reviews but greater responsibility on the part of the IRBs involved.

Third, questions have been raised about the extent and quality of the protections afforded by current informed consent requirements and practices. A variety of critics have highlighted problems with consent forms. In some research studies, consent forms have become lengthy and are often written in highly technical terms.^{24 25 26} Many also claim that consent forms have evolved to protect institutions rather than to actually provide salient information to potential human subjects.²⁷ This is especially problematic if the forms fail to include information that is crucial for making a decision about participation, including appropriate information about financial relationships between researchers and study sponsors, or are written in a way that potential subjects are likely to fail to notice such information. At the same time, others raise concerns about the rigid application of written consent to all forms of research, especially research involving surveys, interviews, focus groups, or other similar methodologies.²⁸ In these types of research, it has been argued that written documentation of consent is unnecessary and that answering questions should be sufficient to indicate individual consent to participate.²⁹

Fourth, increasing use of genetic information, existing (*i.e.*, stored) biospecimens, medical records, and administrative claims data in research has changed the nature of the risks and

benefits of research participation. Risks related to these types of research are not physical but informational (e.g., resulting from the unauthorized release of information about subjects). The Privacy Rule promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA)³⁰ addresses some of these informational risks by imposing restrictions on how certain identifiable health information collected by health plans, healthcare clearinghouses, and certain healthcare providers (“covered entities”) may be used and disclosed, including for research. In addition, the HIPAA Security Rule 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 (or business associates of a covered entity). Separate from the HIPAA Rules, the Privacy Act of 1974, as amended (5 U.S.C. 552a³¹) requires Federal agencies to protect personally identifiable information in their possession and control. However, it does not apply to non-Federal researchers.

Fifth, the monitoring and evaluation of the current system for protecting human subjects has been criticized.³² There is concern that current regulations do not provide an ideal mechanism for the collection of information that would allow evaluation of the effectiveness of the research oversight system in protecting human subjects.

Sixth, concerns have been expressed that the current regulatory system does not adequately protect all research subjects.³³ For instance, only some research studies funded by certain Federal agencies or those that involve the development of products subject to regulation by the FDA, are subject to the Common Rule or similar protections. As a result, there are many studies that are not subject to any such Federal oversight, even though they may involve substantial risks to the subjects.

Seventh, the multiple, differing regulatory requirements that can apply to a single research study have been criticized as complex, inconsistent, and lacking in clarity, which results in unwarranted variability across institutions and their IRBs in how the requirements are interpreted and implemented.³⁴ For example, Federal agencies that have adopted the Common Rule have issued guidance and developed norms of implementation

that sometimes differ and may, in certain instances, even conflict with guidance from other Common Rule agencies. Similarly, the overlapping and sometimes, arguably, inconsistent requirements of the Common Rule and the HIPAA Privacy Rule have been criticized as being overly complex, causing confusion and frustration among investigators, IRBs, and others trying to comply with both sets of requirements.³⁵

In response to these various criticisms, we propose changes to the following seven aspects of the current regulatory framework. The fundamental goal is to enhance the effectiveness of the research oversight system by improving the protections for human subjects while also reducing burdens, delays, and ambiguity for investigators and research subjects.

1. Refinement of the existing risk-based regulatory framework (Section II);
2. Utilization of a single IRB review of record for domestic sites of multi-site studies (Section III);
3. Improvement of consent forms and the consent process (Section IV);
4. Establishment of mandatory data security and information protection standards for all studies that involve identifiable or potentially identifiable data (Section V);
5. Establishment of an improved, more systematic approach for the collection and analysis of data on unanticipated problems and adverse events (Section VI);
6. Extension of Federal regulatory protections to all research, regardless of funding source, conducted at institutions in the U.S. that receive some Federal funding from a Common Rule agency for research with human subjects (Section VII); and
7. Improvement in the harmonization of regulations and related agency guidance (Section VIII).

We believe the proposals we are considering uphold and better reflect the ethical principles upon which the Common Rule is based. We recognize that this ANPRM is both lengthy and detailed. However this level of detail reflects the importance and types of changes that have been proposed by the Institute of Medicine (IOM), NBAC, and other commentators and are now being considered for adoption. Comment is now sought on these proposals and on the broader question of how to modernize, simplify, and enhance the current system. The intent is to revise the Common Rule³⁶ recognizing that other laws and regulations, such as the other subparts of the HHS human subjects protection regulations (Subparts B, C, and D, which deal with

particular populations of vulnerable subjects, and Subpart E of 45 CFR part 46), FDA regulations, and the HIPAA Privacy Rule most likely will be affected and will need to be harmonized, as appropriate, with any proposed regulatory changes made to the Common Rule.

As we consider how the current regulations governing human subjects research should be revised, we will take into account the deliberations of the Presidential Commission for the Study of Bioethical Issues. We will also consider the public comments received on the request for information that the Commission issued 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.³⁷

II. Ensuring Risk-Based Protections

Currently, the Common Rule provides for several tiers of independent review of research studies, as follows:

1. The highest level of review, applied to most studies involving more than minimal risk and to many studies involving no more than minimal risk, is review by a convened IRB.

2. The next level of review is *expedited* review.³⁸ This generally involves review by a single IRB member. A study is eligible for expedited review if the research appears on a list published by the Secretary of HHS of categories of research eligible for such review, and the research is found by the reviewer(s) to involve no more than minimal risk.

3. Certain studies are *exempt* from IRB review.³⁹ The regulations specify six “exemption” categories; a study must fall within one or more of these six categories to be exempted from IRB review altogether. Although these studies are not subject to the Common Rule, and no review is actually required, guidance issued by the Office for Human Research Protection (OHRP) recommends that there be some type of review by someone other than the investigator to confirm that the study qualifies as exempt, and many institutions do indeed impose such a requirement.⁴⁰

There has been criticism about this regulatory framework for reviewing research studies. Although it does attempt to match the level of review to the type of risks posed by a study, many argue that it does so in a less than ideal manner. For instance, many surveys that are unlikely to lead to any harm to subjects nonetheless undergo review by a convened IRB.⁴¹ Further, arguments

have been made that some of the lines drawn between review categories are vague and difficult to apply.⁴² Studies have shown that different levels of review are sometimes required by different IRBs for the same study.^{43 44}

In response to these concerns, the IOM report on research protections recommended revising the current approach: “The degree of scrutiny, the extent of continuing oversight, and the safety monitoring procedures for research proposals should be calibrated to a study’s degree of risk. Minimal risk studies should be handled diligently, but expeditiously, while studies involving high risk should receive the extra time and attention they require.”⁴⁵ The IOM surmised that this would reduce burdens that do not translate into meaningful protections of human subjects and would limit unnecessary drain on resources, enabling IRBs to give more attention to high risk studies and critical protection activities while improving the efficiency with which research projects are reviewed and overseen.

This ANPRM describes potential refinements to the current review framework intended to ensure that protections are commensurate with the level of risk of the research study. Five of the most significant changes being considered are summarized below, followed by a more detailed explanation of the proposals:

1. Establishing mandatory data security and information protection standards for identifiable information and rules protecting against the inappropriate re-identification of de-identified information that is collected or generated as part of a research study to minimize informational risks and thereby eliminate the need for IRBs to review informational risks of the research. For purposes of the Common Rule, we are considering adopting the HIPAA standards regarding what constitutes individually identifiable information, a limited data set, and de-identified information, in order to harmonize these definitions and concepts. Since this provision would cover studies currently considered “exempt” from the current regulations, a change in terminology would need to be considered (see Section B(3), below).

2. Revising the rules for continuing review. Continuing review would be eliminated 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 (i) analyzing data (even if it is identifiable), or (ii) 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).

3. Revising the regulations regarding expedited review to provide for mandatory regular updating of the list of categories of research that may be reviewed under this mechanism, creating a presumption that studies utilizing only research activities that appear on that list are indeed minimal risk, and providing for streamlined document submission requirements for review.

4. Revising the regulations regarding studies currently considered exempt to, among other things:

i. Require that researchers file with the IRB a brief form (approximately one page) to register their exempt studies, but generally allow the research to commence after the filing;

ii. Clarify that routine review by an IRB staff member or some other person of such minimal risk exempt studies is neither required nor even recommended;

iii. Expand the current category 2 exemption (45 CFR 46.101(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 discussed above);

iv. Add 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 discussed above);

v. Expand the current category 4 exemption (regarding the collection or study of existing data, documents, records and biospecimens) (45 CFR 46.101(b)(4)) to include all secondary research use of identifiable data and biospecimens that have been collected for purposes other than the currently proposed research, provided that specified new consent requirements are satisfied. This expanded category 4 exemption would apply to the secondary use of identifiable data and biospecimens even if such data or biospecimens have not yet been collected at the time of the research

proposal, and even if identifiers are retained by the researcher (instead of requiring at least expedited review, as is currently the case); and

vi. Require random retrospective audits of a sample of exempt studies to assess whether the exemptions were being appropriately applied.

5. 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 described in (4), above, and thus would not require IRB review or any routine administrative review but would be subject to the data security and information protection standards discussed above. This change would conform the rules for research use of clinically-collected biospecimens with 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.

Each of these five proposals and other proposed changes are discussed below. We seek comments and recommendations on the specific changes being considered.

A. A New Mechanism for Protecting Subjects From Informational Risks

Most research risks to the individual can be categorized into one of three types: physical, psychological, and informational risks. (Although there are other harms, such as legal, social, and economic harms, these can usually be viewed as variations on those core categories.) Physical risks are the most straightforward to understand—they are characterized by short term or long term damage to the body such as pain, bruising, infection, worsening current disease states, long-term symptoms, or even death. Psychological risks can include unintentional anxiety and stress including feelings of sadness or even depression, feelings of betrayal, and exacerbation of underlying psychiatric conditions such as post traumatic stress disorder. Psychological risks are not

necessarily restricted to psychiatric or social and behavioral research.

Informational risks derive from inappropriate use or disclosure of information, which could be harmful to the study subjects or groups. For instance, disclosure of illegal behavior, substance abuse, or chronic illness might jeopardize current or future employment, or cause emotional or social harm. In general, informational risks are correlated with the nature of the information and the degree of identifiability of the information. The majority of unauthorized disclosures of identifiable health information from investigators occur due to inadequate data security.⁴⁶

Currently, IRBs evaluate all three categories of risk. IRB review or oversight of research posing informational risks may not be the best way to minimize the informational risks associated with data on human subjects. It is not clear that members have appropriate expertise regarding data protections. The current assumption that IRBs are responsible for reviewing and adequately addressing informational risks appears to lead to inconsistent protections and some cases in which there are inadequate protections for the information.⁴⁷ Furthermore, review of informational risk is an inefficient use of an IRB's time. Standardized data protections, rather than IRB review, may be a more effective way to minimize informational risks.

Accordingly, we are considering mandatory standards for data security and information protection whenever data are collected, generated, stored, or used. The level of protection required by these standards would be calibrated to the level of identifiability of the information, which would be based on the standards of identifiability under the HIPAA Privacy Rule. (These standards are discussed in detail in Section V.) With these standards in place to minimize the inappropriate use or disclosure of research information, the criteria for IRB approval of studies would be modified so that an IRB would no longer be responsible for assessing the adequacy of a study's procedures for protecting against informational risks. This change would not alter the IRB's role in assuring that the ethical principles of respect for persons, beneficence and justice are adequately fulfilled.

B. Calibrating the Levels of Review to the Level of Risk

To improve the link between the type of review and the level of risk posed by research studies, we are considering the

changes described below. Since there would be new mandatory standards for data security and information protection to address informational risks, only non-informational risks would be considered in determining the level of risk posed by research studies.

1. Full Convened IRB Review

The requirement that research involving greater than minimal risk be reviewed by a convened IRB would not be changed from the current system. Other changes considered in this ANPRM, such as improvements in the ability of IRBs to require better consent forms, may enhance the effectiveness of such review.

With regard to continuing review of such studies, we are considering one change. Where the remaining activities in a study are limited to either (i) data analysis (even if identifiers are retained) or (ii) accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical problems (such as periodic CT scans to monitor whether the subjects' cancers have recurred or progressed), the default would be that no continuing review by an IRB would be required. The IRB would have the option to make a determination that overrides this default. Researchers would still have the current obligations to report various developments (such as unanticipated problems, or proposed changes to the study) to the IRB. This would be a change from the current rules, which require at least expedited IRB review of the activities described in (i) and (ii) directly above. By eliminating the requirement for continuing review of these activities, 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 protections of research subjects.

2. Revise Approach to Expedited Review

Under the Common Rule, a new 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 (<http://www.hhs.gov/ohrp/policy/expedited98.html>), and is found by the reviewer(s) to involve no more than minimal risk. For research that will receive expedited review, three changes are being considered: (1) Revising the criteria that make research studies eligible for expedited review, (2) eliminating the requirement of routine annual continuing review of expedited

studies, and (3) streamlining submission requirements.

(a) Eligibility for Expedited Review

Currently, a reviewer must determine that the study includes only research activities that appear in the list promulgated by the Secretary as eligible for expedited review, that the study as a whole involves no more than minimal risk, and that all of the criteria listed in 45 CFR 46.111 are met. We are considering changes in each of these three areas:

i. List of Research Activities That Qualify a Study for Expedited Review

We are considering initially updating the current list of research activities, which was last updated in 1998. We also are considering mandating that a standing 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.

ii. Determination That the Study Involves No More Than Minimal Risk

As noted, currently a study can undergo expedited review if all of the activities involved appear on the list of eligible research activities and the study is found to be minimal risk. The current definition of minimal risk 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."⁴⁸ Since the listed activities are ones with which there is a great deal of experience, and their risks are well known, it should be a rare instance in which a study that uses only the listed activities will, as a whole, pose more than minimal risk. Yet many studies which use only those activities—particularly those in the social and behavioral field—are frequently required to undergo review by a convened IRB.⁴⁹ We are accordingly considering providing a default presumption in the regulations that a study which includes only activities on the 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.

iii. Determination That the Study Meets All of the 45 CFR 46.111 Criteria

Given that a study is eligible for expedited review only if it involves minimal risk, and only if its activities are limited to those that appear on the published list, it is not clear that the study should be required to meet all of the criteria for IRB approval at 45 CFR 46.111. 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 following criteria have been satisfied as required by 45 CFR 46.111:

1. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which 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 (for example, 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 involving vulnerable populations, such as children, prisoners, pregnant women, 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 § 46.116.

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

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.

8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, 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.

Accordingly, we are considering whether all of those criteria should still be required for approval of studies that qualify for expedited review, and if not, which ones should not be required.

(b) Eliminating Continuing Review of Expedited Studies

We believe that 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 that it may be preferable for IRB resources to be devoted to research that poses greater than minimal risk.

Accordingly, we are considering changing the default to require no continuing review for studies that qualify for expedited review. Researchers would still be obligated to obtain IRB approval for changes to a study and to report to the IRB unanticipated problems and other similar items that are currently required to be reported.

For any specific study, the reviewer would have the authority to make a specific determination and provide a justification about why continuing review is appropriate for that minimal risk study, and to specify how frequently such review would be required.

(c) Streamlining Documentation Requirements for Expedited Studies

Under the current Federal regulations, researchers typically must submit the same documents including a detailed protocol, informed consent documents, 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. 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.

Ideally, 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 would 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.

Comments and recommendations are requested on any of the above proposals under consideration and on the following specific questions:

Question 1: Is the current definition of “minimal risk” in the regulations (45 CFR 46.102(i)—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”)—appropriate? If not, how should it be changed?

Question 2: Would the proposals regarding continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

Question 4: Should the regulations be changed to indicate that IRBs should only consider “reasonably foreseeable risks or discomforts”?

Question 5: What criteria can or should be used to determine with specificity whether a study's psychological risks or other nonphysical, non-information risks, are greater than or less than minimal?

Question 6: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk? How should the characteristics of the study population (e.g. mental health patients) be taken into consideration in the risk assessment?

Question 7: What research activities, if any, should be added to the published

list of activities that can be used in a study that qualifies for expedited review? Should any of the existing activities on that list be removed or revised? For instance, should the following be included as minimal risk research activities:

- Allergy skin testing.
- Skin punch biopsy (limited to two per protocol).
- Additional biopsy during a clinical test (e.g., performing an extra colonic biopsy in the course of performing a routine colonoscopy).
- Glucose tolerance testing among adults.

Question 8: Should some threshold for radiological exams performed for research purposes, that is calibrated to this background level of exposure, be identified as involving no more than minimal risk?

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?

Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR 46.111 should not apply to a study that qualifies for expedited review?

Question 11: What are the advantages of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow such review to be done by an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB? If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review? If so, what would qualify as being “appropriately trained”? Would the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?

Question 12: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects? Are there specific elements that can be appropriately eliminated from protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? Conversely, are there specific additions to protocols or consent forms beyond those identified in this notice that would meaningfully add to the protection of subjects? What entity or organization should develop and disseminate such standardized document formats?

Question 13: Given the problems with the current system regarding wide variations in the substance of IRB reviews, would it be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the defaults described in Sections B(1), B(2)(a)(ii), and B(2)(b) above? Should IRBs have to report instances in which they require continuing review or convened IRB review of a study which involves only activities identified as being on the list of those eligible for expedited review? If an IRB that chose to override these defaults was required to submit a report to OHRP, would this provide useful information about any lack of appropriate consistency among IRBs so that clarifying guidance could be provided as needed, or provide useful information to OHRP about the possible need to revise the expedited review list or the continuing review requirements?

3. Moving Away From the Concept of Exempt

We are considering revising the category of exempt research in ways that would both increase protections and broaden the types of studies covered. Specifically, although still not subject to IRB review, these studies would be subject to the new data security and information protection standards described in Section V, and in some cases, informed consent would be required as described in Section (c) below. Given that these studies would no longer be fully exempt from the regulations, they could more accurately be described as “Excused” from being required to undergo some form of IRB review (which terminology we will use hereafter in this ANPRM). (Note: FDA’s statute requires IRB review and approval of any clinical device investigation. 21 U.S.C. 360j(g)(3)(A) and (B). Therefore, FDA-regulated studies involving specimens will not be eligible for the new Excused category and will remain subject to IRB oversight.) The new data security and information protection standards make it possible to increase the coverage of the Excused category, thereby reducing the burden on researchers conducting minimal risk studies, while actually increasing the protections for participants.

Some specific aspects of these changes are described here:

(a) Types of Research Studies That Qualify for the Excused Category

The existing six exemption categories would be retained as part of the new Excused category. The current criteria for defining those categories would be

reviewed and revised appropriately so that they are clear enough that researchers could readily determine whether a study qualified to be in these categories. In addition, the following significant expansions of the current categories are being considered:

1. Limitations specified in the current exempt category 2 (research involving educational tests, surveys, focus groups, interviews, and similar procedures) would no longer be necessary when these studies are conducted with competent adults. The current exemption 2 under 45 CFR 46.101(b)(2) states: “Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.” Specifically it is proposed that the language that appears after the word “unless” in provisions (i) and (ii) would be deleted. Thus, research conducted with competent adults, that involve educational tests, surveys, focus groups, interviews, and similar procedures would qualify for the new Excused category, regardless of the nature of the information being collected, and regardless of whether data is recorded in such a manner that subjects can be identified. It is proposed that the limitations on the current category 2 be eliminated since these studies would be conducted with competent adults and because these studies would now be subject to standard data security and information protection standards. The term “competent” as used here and throughout this ANPRM refers to adults who would be able to provide “legally effective informed consent,” as currently required by 45 CFR 46.116. This concept has been included in the Common Rule for decades, and is routinely implemented by researchers, generally with little difficulty. For example, researchers who currently conduct non-exempt surveys must make determinations regarding which subjects to include in their studies, and we are not aware of any evidence that suggests making such determinations has been a problem.

2. We are considering whether to include on the list of Excused studies certain types of social and behavioral research, 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 prior review does little to increase protections to subjects. These would be methodologies which are very familiar to people in everyday life and in which verbal or similar responses would be the research data being collected. For example, a researcher might ask subjects to watch a video, or 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 allow a study to be expedited.

3. Limitations specified in the current exempt category 4 (research involving the use of existing information or biospecimens) would be eliminated. The current exemption 4 under 45 CFR 46.101(b)(4) states: "Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." Specifically, it is proposed that the category would be revised to clarify that the word "existing" means collected for purposes other than the proposed research and not that all of the data or biospecimens need exist at the time the study commenced. In addition, the limitation that the researcher cannot record and retain information that identifies the subjects would be eliminated. In other words, research that only involves the use of data or biospecimens collected for other purposes, even if the researcher intends to retain identifiers, would now come within the new Excused category, unless there are plans to provide individual results back to the subjects. Studies that include a plan to provide to subjects individual results from the analysis of their biospecimens or data would not qualify for this proposed Excused category.

As described below in Section (c), it is contemplated that certain relatively flexible consent requirements would be imposed on some of these studies. (See Table 1 at the end of Section V for a summary of this proposal.)

(b) Tracking and Auditing Excused Research

We are considering a mechanism to track Excused research, and to audit only a small but appropriate portion of such research, because it would still be subject to other regulatory protections, such as the proposed data security and information protection standards and certain consent requirements. In addition, such a mechanism to track and audit Excused research will also enable institutions to assure that the research does indeed meet the criteria for inclusion in the Excused category. (That is all that an audit would in most cases involve: a brief review of the registration form, similar to what many institutions currently do when they determine whether a study is exempt.) Key to this would be a requirement that researchers register their study with an institutional office by completing a brief form. This would make the institution aware of the research and identify the study's principal investigator. In addition the institution could choose to review some of the submissions at the time they are filed (and we contemplate that this would only be done in a relatively small percentage of the filings) and if deemed appropriate, require that the study be sent for expedited review or, in exceptionally rare cases, convened IRB review.

The proposed auditing requirement is intended to encourage institutions to use the regulatory flexibility proposed for the Excused category of research. Rather than maintaining many institutions' current practice of routinely requiring that research that meets the current exemption categories undergo some type of review before it is permitted to proceed, the proposed auditing requirement would provide institutions with information needed to assess their compliance with the new Excused category without unnecessarily subjecting all such research to either prospective review, or even routine review sometime after the study is begun.

(c) Consent Rules for Excused Research

We are contemplating that the consent practices for studies currently designated as exempt would remain in most respects unchanged for research falling within the new Excused category, even if some of those practices are clarified. For example, oral consent without written documentation would continue to be acceptable for many research studies involving educational tests, surveys, focus groups, interviews, and similar procedures.

However, we are considering the following revisions to the consent rules for the category of Excused research that involves the use of *pre-existing data or biospecimens* as described in Section 3(a)(3) above.

First, written general consent (as described below) would be required for the research use of such *biospecimens*. This would be a change from the current rules which 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.

Second, with regard to the researchers' use of *pre-existing data* (*i.e.* data that were previously collected for purposes other than the currently proposed research study):

a. If the data was 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 (see Section V), without obtaining consent.

b. If the data was originally collected for *research* purposes, then consent would be required regardless of whether the researcher 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 data 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.

In most instances, the consent requirements described above would have been met at the time that the biospecimens or data were initially collected, when the subject would have signed a standard, brief general consent form allowing for broad, future 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 anytime by the institution. Importantly, this standardized general consent form would permit the subject to say no to all future research. In addition, 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, would be dealt with by check-off boxes allowing subjects to separately say yes or no to that particular type of research (e.g., perhaps creating a cell line, or reproductive research). 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, it is 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. Table 1 at the end of Section V illustrates the consent requirements for pre-existing data in the context of the data security and information protection requirements which would also apply.

Third, 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.

And fourth, there would be rules (to be determined) 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) Overall Consequences for Current Review Practices

The proposal for changes described in sections (a) through (c) above would eliminate the current practice of not allowing researchers to begin conducting such minimal risk studies until a reviewer has determined the study does indeed meet the criteria for being exempt. Such delay is not currently required by the Common Rule, and appears to slow research without adding significant protection to subjects. Instead, under the plan being considered, researchers would file with their institution or IRB a brief registration form (about one page long) that provides essential information about the study, including, for example, information about who will be the principal investigator, and the purpose of the study. The researchers would then be authorized to begin conducting the study after the filing (unless the institution chose to review that filing and determined that the research did not qualify as Excused). 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 review prior to commencing the study or even afterward.

Comments and recommendations are requested on any of the above proposals under consideration and on the following specific questions:

Question 14: Are these expansions in the types of studies that would qualify for this Excused category appropriate? Would these changes be likely to discourage individuals from participating in research? Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?

Question 15: Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category? Are there specific types of studies that are being considered for inclusion in these expansions, that should not be included because they should undergo prospective review for ethical or other reasons before a researcher is allowed to commence the research?

Question 16: Should research involving surveys and related methodologies qualify for the Excused category only if they do not involve topics that are emotionally charged, such as sexual or physical abuse? If so, what entity should be responsible for determining whether a topic is or is not emotionally charged?

Question 17: What specific social and behavioral research methodologies should fall within the Excused category? Under what circumstances, if any, should a study qualify for the Excused category if the study involves a form of deception (and if so, how should "deception" be defined)?

Question 18: Currently some IRBs make determinations regarding whether clinical results should be returned to study participants. How should such determinations be made if the study now fits in the Excused category? Can standard algorithms be developed for when test results should be provided to participants and when they should not (e.g., if they can be clinically interpreted, they must be given to the participants?)

Question 19: Regarding the Excused category, should there be a brief waiting period (e.g. one week) before a researcher may commence research after submitting the one-page registration form, to allow institutions to look at the forms and determine if some studies should not be Excused?

Question 20: The term "Excused" may not be the ideal term to describe the studies that will come within the proposed revision of the current category of exempt studies, given that these studies will be subject to some protections that are actually greater than those that currently exist. Might a term such as "Registered" better emphasize that these studies will in fact be subject to a variety of requirements designed to protect participants? We welcome other suggestions for alternative labels that might be more appropriate.

Question 21: Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category? Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements? Should some other method besides a random selection be used to determine which Excused studies would be audited?

Question 22: Are retrospective audit mechanisms sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin a study? Might this new audit mechanism end up producing a greater burden than the current system? Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category? By allowing researchers to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened? If allowing researchers to make such determinations without independent review would generally be acceptable, are there nonetheless specific categories of studies included in the proposed expansion for which this change would inappropriately weaken protections for subjects? And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) above? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?

Question 24: The Common Rule has been criticized for inappropriately being applied to—and inhibiting research in—certain activities, including quality improvement, public health activities, and program evaluation studies.^{50 51 52} Regarding quality improvement, for example, these 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. It is far from clear that the Common Rule was intended to apply to such activities, nor that having it apply produces any meaningful benefits to the public. Indeed, its application to such activities, and requiring IRB review and compliance with informed consent requirements, might have a chilling effect on the ability to learn from, and conduct, important types of innovation. We seek comment on whether and, if so, how, the Common Rule should be changed to clarify whether or not oversight of quality improvement, program evaluation studies, or public health activities are covered. Are there specific types of these studies for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of “research” used in the Common Rule to exclude some of these studies, or a combination of both? And if the definition of research were to be changed, how should the activities to be excluded be defined (e.g., “quality improvement” or “program evaluation”)? Are there some such activities that should not be excluded from being subject to the Common Rule because the protections provided by that rule are appropriate and no similar protections are provided by other regulations? With regard to quality improvement activities, might it be useful to adopt the distinction made by the HIPAA Privacy Rule (45 CFR 164.501(1)), which distinguishes between “health care operations” and “research” activities, defining “health care operations” to include “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”?

Question 25: Are there certain fields of study whose usual methods of

inquiry were not intended to or should not be covered by the Common Rule (such as classics, history, languages, literature, and journalism) because they do not create generalizable knowledge and may be more appropriately covered by ethical codes that differ from the ethical principles embodied in the Common Rule? If so, what are those fields, and how should those methods of inquiry be identified? Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?

Question 26: The current exempt category 5 applies to certain research and demonstration projects that are designed to study or evaluate public benefit or service programs. Is the circumstance that a particular demonstration project generates “broad” knowledge incorrectly being used as a reason to prevent certain activities (including section 1115 waivers under Medicaid) from qualifying for exempt category 5? If so, how should this exemption (as part of the new category of Excused research) best be revised to assure that it will no longer be misinterpreted or misapplied? Would broadening the interpretation of the exemption result in inappropriately increased risks to participants in research? If so, how could such risks be mitigated? Also, is there a need to update or otherwise revise the “OPRR Guidance on 45 CFR 46.101(b)(5)”?

Question 27: The Common Rule currently states (45 CFR 46.111(a)(2)) that an IRB “should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among the research risks that fall within the purview of its responsibility.” Do IRBs correctly interpret this provision as meaning that while they should be evaluating risks to the individual subjects participating in a study, it is not part of their mandate to evaluate policy issues such as how groups of persons or institutions, for example, might object to conducting a study because the possible results of the study might be disagreeable to them?⁵³ If that is not how the provision is typically interpreted, is there a need to clarify its meaning?

Question 28: For research that requires IRB approval, the Common Rule does not currently require that the researcher always be allowed some form of appeal of a decision (e.g., disapproval of a project). Some institutions have voluntarily chosen to provide appeal mechanisms in some instances, by, for example, allowing the researcher to present the project to a different IRB, or

by having it reviewed by a special “appeal” IRB that is composed of members chosen from among the membership of the institution’s other IRBs. Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism? If so, what should be considered acceptable appeal mechanisms? Should such appeal mechanisms, or different ones, be available for appeals asserting that the investigation is not research, or that the research does not require IRB approval?

Question 29: As noted above, IRBs sometimes engage in activities beyond those that are required by the regulations. For example, an IRB might review some studies for the purpose of determining whether or not they qualify for exemption (the new Excused category), or might review studies involving the analysis of data that is publicly available. Would it be helpful, in furtherance of increased transparency, to require that each time an IRB takes such an action, it must specifically identify that activity as one that is not required by the regulations?

III. Streamlining IRB Review of Multi-Site Studies

Currently, a substantial amount of research takes place by means of multi-site studies wherein a single research study is conducted at numerous institutions. Multi-site studies are particularly common in clinical trials, survey epidemiology, and education contexts. While the Common Rule does require that each institution engaged in a multi-site research study obtain IRB approval of the study, it does not require that a separate local IRB at each institution conduct such review. (*Note:* While the Common Rule does not require local IRB review by each institution engaged in a multi-site research study, the statute that pertains to FDA’s regulation of device investigations requires sponsors to submit the protocol to the “local institutional review committee which has been established in accordance with regulations of the Secretary to supervise clinical testing of devices in the facilities where the proposed clinical testing is to be conducted.” The only statutory exception is if a local IRB does not exist or its review is determined to be “inadequate” (21 U.S.C. 360j(g)(3)(A)). Accordingly, the change proposed in this ANPRM regarding the use of one IRB of record for multi-site studies would not apply to FDA-regulated device studies.) However, in many cases, a local IRB for each institution does independently review the research protocol, informed consent

documents 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. Separately, there are reports showing that there can be widely differing outcomes regarding the level of review required from IRB to IRB, even for identical studies.⁵⁴

The choice to have multi-site research reviewed by a central IRB, or by an IRB at another institution, is voluntary. In practice, most institutions have been reluctant to replace review by their local IRBs with review by a central IRB.^{55 56} Participants in two meetings on alternative IRB models that OHRP co-sponsored 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, even in circumstances when the regulatory violation is directly related to the responsibilities of an external IRB.⁵⁷

Many commentators⁵⁸ claim that multiple IRB reviews do not enhance the protection of human subjects and may, in fact, divert valuable resources from more detailed reviews of other studies. Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most clinical 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 document and process generally do not require the unique perspective of a local IRB.

To respond to this concern, central IRBs have been developed. The National Cancer Institute created a central IRB for adult research studies in 2001 and a central pediatric oncology IRB in 2004. Similarly, the Department of Veterans Affairs has required review of certain multi-site protocols by a single national IRB since 2008. Also, certain groups of private institutions have joined together to develop their own central IRBs. These

central IRBs reduce the workload for local IRBs and may minimize institutional conflicts of interest. Since 2006, FDA has endorsed the use of a centralized IRB review process in multi-site clinical trials of investigational new drugs and has issued guidance intended to assist sponsors, institutions, IRBs, and clinical investigators on its implementation.⁵⁹

Public comment is requested on the feasibility, advantages, and disadvantages of mandating that all domestic sites in a multi-site study rely upon a single IRB as their IRB of record for that study. (This would apply regardless of whether the study underwent convened review or expedited review.) This proposal would only affect which IRB would be designated as the IRB of record 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 (and could be discouraged). To address institutions' concerns about OHRP's practice of enforcing compliance with 45 CFR part 46 through the institutions that are engaged in human subjects research, appropriate accompanying changes would be made in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory requirements (see, e.g., the proposal on IRB accountability released by OHRP in 2009, at <http://www.hhs.gov/ohrp/newsroom/rfc/com030509.html>)

This change is being considered only for domestic sites in multi-site studies. 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.

Comments and recommendations are requested on the following:

Question 30: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances

protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's specific perspective or the needs of their population, or that a centralized IRB may not share an institution's views or interpretations on certain ethical issues?

Question 32: To what extent are concerns about regulatory and legal liability contributing to institutions' decisions to rely on local IRB review for multi-site research? Would the changes we are considering adequately address these concerns?

Question 33: How significant are the inefficiencies created by local IRB review of multi-site studies?

Question 34: If there were only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of "IRB shopping"—intentionally selecting an IRB that is likely to approve the study without proper scrutiny—be prevented?

IV. Improving Informed Consent

Currently, under the Common Rule and FDA regulations, investigators generally must obtain and document the subjects' informed consent to participate in research.⁶⁰ 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 has the amount of time IRBs devote to editing and revising consent forms.

In addition, consent forms may frequently fail to include some of the most important pieces of information that a person would need in order to make an "enlightened decision" (to quote the Nuremberg Code) to enroll in a research study.⁶¹ 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, instead of as genuine aids to good decision-making.⁶²

While the regulations have changed in only relatively modest ways since 1974, the average length of consent forms has been increasing since then,⁶³ and the forms have become excessively long and legalistic, even for relatively routine and low risk research studies.⁶⁴ For example, it is not uncommon for the documents to stretch to 15 or even 30 pages in length. Moreover, studies have shown that the reading level of many of these documents is above the desired 8th grade level.^{65 66 67} Length and high reading levels may inhibit people from reading the full document and from understanding relevant information.

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 inconsistent application.⁶⁸ 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 documents and process.

A. Improving Consent Forms

We are considering a number of modifications to the regulations to improve consent forms, including (1) prescribing appropriate content that must be included in consent forms, with greater specificity than is provided in the current regulations; (2) restricting content that would be *inappropriate* to include in consent forms; (3) limiting the acceptable length of various sections of a consent form; (4) prescribing how information should be presented in consent forms, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form; (5) reducing institutional “boilerplate” in consent forms (that is, standard language that does little to genuinely inform subjects, and often is intended to primarily protect institutions from lawsuits); and (6) making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions.

Comments and recommendations are requested on the following:

Question 35: What factors contribute to the excessive length and complexity of informed consent forms, and how might they be addressed?

Question 36: What additional information, if any, should be required by the regulations to assure that consent forms appropriately describe to subjects, in concise and clear language, alternatives to participating in the research study and why it may or may not be in their best interests to participate? What modifications or deletions to the required elements would be appropriate?

Question 37: Would the contemplated modifications improve the quality of consent forms? If not, what changes would do so?

Question 38: Should the regulations require that, for certain types of studies, investigators assess how well potential research subjects comprehend the information provided to them before

they are allowed to sign the consent form?

Question 39: If changes are made to the informed consent requirements of the Common Rule, would any conforming changes need to be made to the authorization requirements of the HIPAA Privacy Rule?

Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required? For example, should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?

B. Waiver of Informed Consent or Documentation of Informed Consent in Primary Data Collection

Currently the Common Rule permits an IRB to waive the requirements for obtaining informed consent under two sets of circumstances (45 CFR 46.116 (c) or (d)).⁶⁹ The most common set of circumstances requires that four specific criteria be satisfied (45 CFR 46.116(d)). Many commentators have argued that these conditions for waiver of consent are vague and applied haphazardly at different institutions.^{70 71} In response to these concerns, the Secretary’s Advisory Committee on Human Research Protections (SACHRP), through its Subcommittee on Subpart A, developed several recommendations regarding the interpretation of these waiver criteria.⁷²

IRBs, under the Common Rule (45 CFR 46.117(c)), also 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. It is worth noting that for studies that only involve surveys, focus groups, and interviews with competent adults, there will usually be no need to apply the waiver of documentation criteria provided at 45 CFR 46.117(c). Such studies will generally qualify for the new Excused category, with only oral consent required.

Comments and recommendations are requested on the following:

Question 41: What changes to the regulations would clarify the current four criteria for waiver of informed consent and facilitate their consistent application?

Question 42: In circumstances where the regulations would permit oral consent, what information should

investigators be required to provide to prospective subjects? Are all of the elements of informed consent included at 45 CFR 46.116 necessary to be conveyed, or are some elements unnecessary? If some elements should not be required for oral consent, which ones are unnecessary?

Question 43: Are there additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent?

Question 44: Are there types of research involving surveys, focus groups, or other similar procedures in which oral consent without documentation should not be permitted? What principles or criteria distinguish these cases?

C. Strengthening Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens

Critics of the existing rules have observed that the current requirements for informed consent for future research with pre-existing data and biospecimens are confusing and consume substantial amounts of researchers’ and IRBs’ time and resources. Under the Common Rule and the HIPAA Privacy Rule, if identifiers are removed, specimens and data that have been collected for purposes other than the proposed research can be used without any requirement for informed consent or a HIPAA authorization. When these identifiers have not been removed, under the Common Rule, investigators may be allowed in certain situations to obtain a general consent for future research with existing biospecimens and other information stored in databases. Conversely, the Department’s current interpretation of the HIPAA Privacy Rule requires that authorizations for research be study-specific. Thus, the Privacy Rule currently has not been interpreted to permit general authorizations for future unspecified research uses of health information. Importantly, the HHS Office for Civil Rights (OCR) has recently sought and is currently reviewing public comment on the extent to which a single general authorization may cover a range of future research uses of an individual’s health information (see 75 FR 40868, 40893 available at <http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/nprmhitech.pdf>).

Because biospecimens and data 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 reuse of existing data 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. As the IOM recently stated in *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*, it is important to “facilitate important health research by maximizing the usefulness of patient data associated with biospecimens banks and in research databases, thereby allowing novel hypotheses to be tested with existing data and materials as knowledge and technology improve.”⁷³

Some critics, including potential and former research subjects, object to research performed on a person’s biospecimens without consent. This was recently highlighted in the book, *The Immortal Life of Henrietta Lacks*.⁷⁴ Conversely, investigators are concerned that the need for informed consent for every use of a biospecimen will greatly inhibit research.^{75 76 77} They worry that obtaining individual consent for each separate research study will create unmanageable logistical demands, making valuable research impossible. They also worry that research will be skewed by individuals who refuse consent, undermining the scientific validity of the research. An accumulating body of data indicates that while most individuals want to be able to decide whether their biospecimens are available for research, they often do not desire to have control over which specific researchers use their samples, for which diseases, at which institutions.^{78 79 80}

The potential changes to the consent rules that were described in detail in Section II(B)(3)(c) (in the discussion of revising the rules for exempt studies) are being considered to strengthen and align consent protections, simultaneously addressing the concerns of individuals, while ensuring the pursuit of important research.

Comments and recommendations are requested on any of the above proposals under consideration and on the following specific questions:

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent? Should consent requirements vary based on the likelihood of identifying a research subject? Are there other circumstances in which it should not be necessary to obtain additional consent for the research use of currently available data that were collected for a purpose other than the currently proposed research?

Question 46: Under what circumstances should unanticipated future analysis of data that were collected for a different research purpose be permitted without consent? Should consent requirements vary based on the likelihood of identifying a research subject?

Question 47: Should there be a change to the current practice of allowing research on biospecimens that have been collected outside of a research study (i.e. “left-over” tissue following surgery) without consent, as long as the subject’s identity is never disclosed to the investigator?

Question 48: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens?

Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?

Question 50: What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens? How should the consent categories that might be contained in the standardized consent form be defined (e.g. an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

Question 51: If the requirement to obtain consent for all research uses of biospecimens is implemented, how should it be applied to biospecimens that are collected outside of the U.S. but are to be used in research supported by a Common Rule agency? Should there be different rules for that setting, and if so, what should they be? Should they be based on the relevant requirements in the countries where the biospecimens were collected?

Question 52: Should the new consent rules be applied only prospectively, that is, should previously existing biospecimens and data sets be “grandfathered” under the prior regulatory requirements? If so, what are the operational issues with doing so?

Question 53: In cases in which consent for future research use is not

obtained at the time of collection, should there be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable, such that consent could be waived, when more than a specified threshold number of individuals are involved? (SACHRP provided the Secretary with recommendations on this issue.⁸¹) If so, what threshold number should constitute impracticability? Is the number of potential human subjects the only measure of impracticability?

V. Strengthening Data Protections To Minimize Information Risks

Collection of identifiable data, as well as secondary analyses of such data, poses informational risks. The assurance that identifiable information will be safeguarded is important for an individual’s willingness to participate in research. Further, we recognize that there is an increasing belief that what constitutes “identifiable” and “de-identified” data is fluid; rapidly evolving advances in technology coupled with the increasing volume of data readily available may soon allow identification of an individual from data that is currently considered de-identified. In this sense, much of what is currently considered de-identified is also potentially identifiable data.

While there are currently some regulatory approaches that can be used to safeguard and maintain the confidentiality of research participants’ information, such protections are limited in scope. The HIPAA Privacy and Security Rules generally require safeguards for individually identifiable health information and place limits and conditions on the use and disclosure of such information. However, the Rules only apply to researchers if they are part of a HIPAA covered entity (e.g., a covered health care provider or health plan) and, to a certain extent, to researchers that are business associates of a covered entity.

Separate from the HIPAA Rules, the Privacy Act of 1974, as amended (5 U.S.C. 552a⁸²) binds Federal agencies to protect personally identifiable information in their possession and control. It prohibits the disclosure (without prior consent or notice) of records that are retrieved by personal identifiers. In addition, there are other Federal privacy provisions that may need to be considered, but all have a limited scope. For example, Title 5 of the E-Government Act,⁸³ entitled the “Confidential Information Protection and Statistical Efficiency Act of 2002,” (CIPSEA) provides additional protections for confidential statistical

information collected by the Federal government. However, neither the Privacy Act nor CIPSEA generally apply to grant-funded investigators who are neither Federal employees nor contractors. (An additional example is the Department of Justice's set of regulations for protecting information collected in certain research and other programs, at 28 CFR part 22.)

Furthermore, none of these statutes was written with an eye toward the advances that have come in genetic and information technologies that make complete de-identification of biospecimens impossible and re-identification of sensitive health data easier. Certificates of confidentiality may be issued upon request through the authority of HHS (section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)) to any investigator conducting IRB-approved research that involves the collection of sensitive and identifiable information. However, certificates of confidentiality do not *require* investigators to refuse to disclose identifying information; rather, they convey the legal *right* to refuse to disclose. Certificates of confidentiality also do not protect against unauthorized or accidental disclosures of identifiable private information due to inadequate data security procedures. The National Institute of Justice (NIJ) provides a different model for privacy protection: all NIJ-funded investigators collecting identifying information must apply for a privacy certificate and are required to keep identifiable data confidential (28 CFR part 22).

Consequently, other fundamental protections for research participants may be warranted beyond updating the requirements for independent review and informed consent currently provided by the Common Rule. As noted above (Section II(A)), a solution we are considering is to mandate data security and information protection standards that would apply to all research that collected, stored, analyzed or otherwise reused identifiable or potentially identifiable information. This would include research with biospecimens, survey data, and research using administrative records as well as secondary analysis of the data. However, we are considering applying these new protections only to prospective collections of data and biospecimens after the implementation of any changes to the Common Rule and not retrospectively to research involving existing data, including stored biospecimens and their subsequent analysis. Further, it is envisioned that these data security and information protection standards would be scaled

appropriately to the level of identifiability of the data.

While the discussion below focuses on these data security and information protection standards, we also are interested in whether there are other changes that might be made to the Common Rule, such as appropriate limitations on researchers' disclosure of identifiable or potentially identifiable information, that would strengthen, and create more uniformity in, the promises of confidentiality that currently exist for human subjects.

A. Consistently Characterizing Information With Respect to Potential for Identification

Currently, the HIPAA Privacy Rule's standards for identifiable and de-identified information are not aligned with what is considered human subjects research under the Common Rule. Under the Common Rule research does not involve "human subjects" if the investigator does not obtain data about individuals through an interaction or intervention or obtain identifiable private information about individuals.⁸⁴ Under the regulatory definition of human subject, "private information" is described as "information about behavior that occurs in a context in which the individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record)." 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. Under the HIPAA Privacy Rule, health information is de-identified and thus exempt from the Rule, if it neither identifies nor provides a reasonable basis 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)). Under these rules, some information that is not considered identifiable under the Common Rule may be considered identifiable for purposes of the HIPAA Privacy Rule, such as dates of service or zip codes.

However, to accommodate investigators' need to have access to data elements such as these, the Privacy Rule also provides for a *limited data set* to be used for research purposes, which is data that has been stripped of direct identifiers but that may retain certain elements, such as dates of service and zip codes (45 CFR 164.514(e)(2)). Because a limited data set is not considered fully de-identified, the Privacy Rule requires that a covered entity enter into a data use agreement with the investigator to prohibit the re-identification of the information and to otherwise protect the information.

We are considering adopting the HIPAA standards for purposes of the Common Rule regarding 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. Furthermore, in light of emerging technologies and evolving informational risks, it might be advisable to evaluate the set of identifiers that must be removed for a data set to be considered "de-identified" under both human subjects regulations and the HIPAA Privacy Rule. Table 1 in Section II illustrates how the HIPAA Privacy Rule's standards of identifiability would apply to the Excused category of research involving pre-existing information or biospecimens.

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. Consequently, we are considering categorizing all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information (see Table 1, at the end of this section).

Comments and recommendations are requested on the following:

Question 54: Will use of the HIPAA Privacy Rule's standards for identifiable and de-identified information, and limited data sets, facilitate the implementation of the data security and information protection provisions being considered? Are the HIPAA standards, which were designed for dealing with health information, appropriate for use in all types of research studies, including social and behavioral research? If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?

Question 55: What mechanism should be used to regularly evaluate and to recommend updates to what is

considered de-identified information? Beyond the mere passage of time, should certain types of triggering events such as evolutions in technology or the development of new security risks also be used to demonstrate that it is appropriate to reevaluate what constitutes de-identified information?

Question 56: DNA extracted from de-identified biospecimens can be sequenced and analyzed in other ways, with the results sometimes being linked to other available data than may allow a researcher to identify the persons whose specimens were being studied. How should Federal regulations manage the risks associated with the possibility of identification of such biospecimens? Should a human biospecimen be considered identifiable in and of itself? What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?

Question 57: Should some types of genomic data be considered identifiable and, if so, which types (e.g., genome-wide SNP analyses or whole genome sequences)?

B. Standards for Data Security and Information Protection

The goal of information protection is to prevent breach of confidentiality through unauthorized access, inappropriate disclosure, or re-identification at either the individual or in some cases the subgroup level. Information that contains direct identifiers of individuals poses a greater informational risk than does a limited data set, which in turn poses a greater informational risk than de-identified information.

As discussed in Section II(A), the majority of unauthorized disclosures of identifiable health information from investigators occur due to inadequate data security.⁸⁵ IRB review or oversight of research posing informational risks may not be the best way to minimize the informational risks associated with data on human subjects. Instead, informational risks may be best mitigated through compliance with stringent standards for data security and information protection that are effectively enforced through mechanisms such as periodic random audits.

We are considering three specific requirements that could strengthen the protections for research studies that pose informational risks. First, research involving the collection and use of identifiable data, as well as data in limited data set form, could be required to adhere to data security standards modeled on the HIPAA Security Rule.⁸⁶

In particular, for research involving individually identifiable information, all biospecimens, and limited data sets, data security standards could require the use of reasonable and appropriate encryption for data maintained or transmitted in electronic form and strong physical safeguards for information maintained in paper form, audit trails, and access controls that allow only authorized personnel to have access to the information. Further, investigators would be required to adhere to breach notification standards modeled on those applied to HIPAA covered entities for breaches of individually identifiable health information.⁸⁷ For research using limited data sets or de-identified information, investigators would be strictly prohibited from attempting to re-identify the subjects of the information. Requiring that investigators implement and adhere to these standard data security and information protection measures would lessen the need for investigators to enter into data use agreements to protect the limited data set, as is currently required under the HIPAA Privacy Rule. Because these mandatory protections would apply to all research studies, it should not be necessary for IRBs to review studies posing only informational risks or to consider informational risks in studies involving other risks to human subjects.

Second, data could be considered de-identified or in limited data set form even if investigators see the identifiers but do not record them in the permanent research file. To de-identify information or create limited data sets, many investigators have established complex procedures for having “trusted third parties” remove identifiers prior to passing on information to an investigator for a study. This adds another level of complexity and suggests that third parties are more trusted to protect information than investigators. If investigators adhere to the standards for data security and information protection there may be less need for these complex third party relationships.

Third, to strengthen the enforcement mechanisms under the Common Rule, we are considering providing for periodic random retrospective audits, and additional enforcement tools.

Comments and recommendations are requested on any of the above proposals under consideration and on the following specific questions:

Question 58: Should the new data security and information protection standards apply not just prospectively to data and biospecimens that are collected after the implementation of new rules, but instead to all data and

biospecimens? Would the administrative burden of applying the rule to all data and biospecimens be substantially greater than applying it only prospectively to newly collected information and biospecimens? How should the new standards be enforced?

Question 59: Would study subjects be sufficiently protected from informational risks if investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules? Are such standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research? Or might a better system employ different standards for different types of research? (We note that the HIPAA Rules would allow subjects to authorize researchers to disclose the subjects’ identities, in circumstances where investigators wish to publicly recognize their subjects in published reports, and the subjects appreciate that recognition.)

Question 60: Is there a need for additional standardized data security and information protection requirements that would apply to the phase of research that involves data gathering through an interaction or intervention with an individual (e.g. during the administration of a survey)?

Question 61: Are there additional data security and information protection standards that should be considered? Should such mandatory standards be modeled on those used by the Federal government (for instance, the National Institute of Standards and Technology recently issued a “Guide to Protecting the Confidentiality of Personally Identifiable Information.”)?

Question 62: If investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, is it then acceptable for HIPAA covered entities to disclose limited data sets to investigators for research purposes without obtaining data use agreements?

Question 63: Given the concerns raised by some that even with the removal of the 18 HIPAA identifiers, re-identification of de-identified datasets is possible, should there be an absolute prohibition against re-identifying de-identified data?

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-identifying such data a sufficient protection, or should there in some instances be requirements preventing the researcher from disclosing the de-identified data to, for example, third

parties who might not be subject to these rules?
Question 65: Should registration with the institution be required for analysis of de-identified datasets, as was proposed in Section II(B)(3) for Excused

research, so as to permit auditing for unauthorized re-identification?
Question 66: What entity or entities at an institution conducting research should be given the oversight authority to conduct the audits, and to make sure

that these standards with regard to data security are being complied with?
 Should an institution have flexibility to determine which entity or entities will have this oversight responsibility for their institution?

TABLE 1—PROPOSAL FOR THE EXCUSED CATEGORY OF RESEARCH INVOLVING PRE-EXISTING INFORMATION OR BIOSPECIMENS

	Identifiable information and all biospecimens	Limited data set (as defined in the HIPAA Privacy Rule)	De-identified information (as defined in the HIPAA Privacy Rule)
Written consent required for future research with material collected for <i>non-research purposes</i> ?	Yes, which could be obtained in connection with the initial collection.	No consent required	No consent required.
Consent for future research with material collected for <i>research purposes</i> ?	Yes. Consent for future research typically obtained at the same time as consent for initial research (which, for data, could be oral when oral consent was permissible for the initial collection).	Yes. Same rule as for “Identifiable Information and All Biospecimens”.	Yes. Same rule as for “Identifiable Information and All Biospecimens.”
Standardized Data Protections?* ...	Yes. Protections would include encryption, use only by authorized personnel with audit tracing, prompt breach notification, and periodic retrospective random audits.	Yes. Same rule as for “Identifiable Information and All Biospecimens” plus a prohibition against re-identification.	Yes. Protection would include prohibition on re-identification.
Registration of research with IRB or research office?.	Yes	Yes	No.
Prior Review by IRB or research office?	No, unless investigators plan to re-contact subjects with their individual research results.	No	No.

*These data protections are discussed in the context of secondary research uses of biospecimens and data, which present mostly informational risks, rather than physical risks, to participants. However, as indicated elsewhere in this ANPRM, informational risks will always be present where data and biospecimens are collected, thus requiring these data protections to be applied to any such research.

VI. Data Collection To Enhance System Oversight

Research agencies collect various types of safety data with the common goal of protecting human subjects. However, individual agency requirements for reporting such data vary. This has resulted in variations between agencies regarding their policies and requirements for the reporting of such data. For example, the Common Rule does not require investigators to report “adverse events”, but rather references “unanticipated problems involving risks to subjects or others.” The relationship of “unanticipated problems” to “adverse events” historically has been unclear. Furthermore, there are some agencies that do require the reporting of many “adverse events” beyond those that constitute “unanticipated problems.” Those reporting requirements often utilize variable definitions of what constitutes such an event and require these reports on different timeframes and on various templates utilizing inconsistent vocabularies describing the severity and nature of these events.

The adverse event data collected by each agency are stored and maintained

in separate datasets. The lack of connectivity and interoperability inhibits the conduct of integrated analyses and comparative studies about the frequency and severity of adverse events. Similarly, current policy requirements and current data collection practices do not foster the collection of data about the numbers of participants in various areas of research—information that is needed for characterizing the magnitude and severity of any risks.

We are considering a number of changes to improve the current system for the real-time prompt collection of such data. These changes are intended to simplify and consolidate the reporting of information that is *already required* to be promptly reported by an investigator, and *not* to expand the information that has to be reported. These changes involve (1) Using a standardized, streamlined set of data elements that nonetheless are flexible enough to enable customized safety reporting and compliance with most Federal agency reporting requirements; (2) implementing a prototype of a Web-based, Federal-wide portal (already developed by NIH, FDA, and 4 other

Federal agencies) that would build on these data elements and allow investigators to submit electronically certain pre- and post-market safety data and automatically have it delivered to appropriate agencies and oversight bodies; and (3) harmonizing safety reporting guidance across all Federal agencies, including harmonizing terminology and clarifying the scope and timing of such reports. In addition to these changes, the Federal government is also considering creating a central Web-based repository to house a great deal of the information collected through the portal.

These innovations create the possibility of eliminating much of the existing multiplicity of different and confusing reporting mechanisms, and could foster greater uniformity and comparability among the safety information that gets reported. Consolidation of data reported using consistent vocabularies and terms would allow for more powerful and meaningful analyses of safety information across types of research studies than are possible at present.

Comments and recommendations are requested on any of the above proposals

under consideration and on the following specific questions:

Question 67: Is the scope of events that must be reported under current policies, including the reporting of certain “unanticipated problems” as required under the Common Rule, generally adequate?

Question 68: With regard to data reported to the Federal government:

a. Should the number of research participants in Federally funded human subjects research be reported (either to funding agencies or to a central authority)? If so, how?

b. What additional data, not currently being collected, about participants in human subjects research should be systematically collected in order to provide an empirically-based assessment of the risks of particular areas of research or of human subjects research more globally?

c. To what types of research should such a requirement apply (*e.g.*, interventional studies only; all types of human subjects research, including behavioral and social science research)? In addition, are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subjects protection system?

Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subjects protections. Toward that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?

Question 70: Clinical trials assessing the safety and efficacy of FDA-regulated medical products (*i.e.*, phase II through IV studies) are generally required to register and, following study completion, report summary results, including adverse events, in the publicly accessible database ClinicalTrials.gov. Is the access to information on individual studies provided by this resource sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human participants?

VII. Extension of Federal Regulations

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 Federalwide Assurance (FWA) or another assurance of compliance approved by the 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 their FWAs 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. However, such extension is not required.

The IOM and NBAC, among many others, have called for legislation that would extend the Common Rule protections to all research with human subjects conducted in the U.S., regardless of funding source.

We are considering an alternative regulatory proposal to partially fulfill this goal: requiring domestic institutions that receive some Federal funding from a Common Rule agency for research with human subjects to extend the Common Rule protections to all research studies conducted at their institution.

Comments and recommendations are requested on the following:

Question 71: Should the applicability of the Common Rule be extended to all research that is *not* Federally funded that is being conducted at a domestic institution that receives some Federal funding for research with human subjects from a Common Rule agency?

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

From the outset of the development of the Common Rule, the importance of consistency across the Federal government has been recognized. In May 1982, the Chairman of the Federal Coordinating Council for Science, Engineering, and Technology appointed an Ad Hoc Committee for the Protection of Human Research Subjects. In consultation with OSTP and the Office of Management and Budget, the Ad Hoc Committee agreed that uniformity is desirable among departments and agencies to eliminate unnecessary regulation and to promote increased understanding and ease of compliance by institutions that conduct Federally supported or regulated research involving human subjects. By 1991, 15 Federal departments and agencies had adopted the Common Rule.

However, each of the departments and agencies that have adopted the Common Rule may issue its own guidance regarding the protection of human subjects. Consequently, there are variations in the guidances issued.

In addition, other Federal laws and regulations have been enacted that relate to the protection of human

subjects, most prominently, the research provisions of the HIPAA Privacy Rule. However, since the HIPAA regulations were developed mainly for the clinical context,⁸⁸ the rules are inconsistent with the Common Rule in certain areas. As noted above, one such inconsistency is the definition of identifiable data and another is the manner in which the two rules treat consent for future research.

Currently, there are multiple efforts to address such variation in guidance across the Federal government. The Common Rule departments and agencies have procedures for sharing proposed guidance before it is adopted. FDA and OHRP have been working closely on enhancing harmonization of guidance.

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, 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 guidances. Not only do the agencies have different relationships to the research, they 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.

Comments and recommendations are requested on the following:

Question 72: To what extent do the differences in guidance on research protections from different agencies either strengthen or weaken protections for human subjects?

Question 73: To what extent do the existing differences in guidance on research protections from different agencies either facilitate or inhibit the conduct of research domestically and internationally? What are the most important such differences influencing the conduct of research?

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally? Would a single set of guidance be able to adequately address human subjects protections in diverse populations and

contexts, and across the broad range of research contexts (including biomedical, national security, education and other types of social and behavioral research)?

IX. Agency Request for Information

When submitting responses to the specific questions asked in this notice, please cite the specific question by number.

In addition to the specific solicitation of comments throughout this ANPRM, general comment is invited on the current system of protections for human research subjects as implemented through the Common Rule, the HIPAA Privacy and Security Rules, and any other rules, regulations or guidance documents. In particular, comments are sought not only on ways to improve the efficiency of the current system, but about circumstances in which the protections provided by the current system might be inadequate and in need of supplementation or change in order to make sure that subjects are receiving appropriate protections.

Dated: July 20, 2011.

John Holdren,

Director, Office of Science Technology and Policy.

Kathleen Sebelius,

Secretary, HHS.

¹ The Federal Policy for the Protection of Human Subjects or the "Common Rule" was published in 1991 and codified in separate regulations by 15 Federal departments and agencies, as listed below (each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that are identical to those of 45 CFR part 46, subpart A).

These agencies included the Department of Agriculture (7 CFR part 1c), Department of Commerce (15 CFR part 27), Department of Defense (32 CFR part 219), Department of Education (34 CFR part 97), Department of Energy (10 CFR part 745), Department of Health and Human Services (45 CFR part 46 subpart A), Department of Housing and Urban Development (24 CFR part 60), Department of Justice (28 CFR part 46), Department of Veterans Affairs (38 CFR part 16), Department of Transportation (49 CFR part 11), Consumer Product Safety Commission (16 CFR part 1028), Environmental Protection Agency (40 CFR part 26), Agency for International Development (22 CFR part 225), National Aeronautics and Space Administration (14 CFR part 1230), National Science Foundation (45 CFR part 690).

In addition, the Central Intelligence Agency must comply with all subparts of 45 CFR part 46 under Executive Order 12333, and in accordance with the Intelligence Reform and Terrorism Protection Act of 2004 (Pub. L. 108-458, Section 8306), the Department of Homeland Security adopted policies implementing the protections for human research subjects under 45 CFR part 46 for research it conducts or supports.

For all participating departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. HHS has developed additional regulations for the human subjects research it conducts or supports that apply to particular special populations: 45 CFR part 46 subparts B-D apply to research involving pregnant women, human fetuses, and neonates (subpart B), prisoners (subpart C), and children (subpart D).

² Congressional Budget Office. *Research and Development in the Pharmaceutical Industry*. October 2006.

³ Ferman DD, Hanna KE, Rodriguez LL, eds. *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, DC: National Academies Press; 2002.

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⁶⁹ Under 45 CFR 46.116(c), an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent otherwise required under 45 CFR part 46, or waive the requirement to obtain informed consent provided the IRB finds and documents that: (1) 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: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and (2) The research could not practicably be carried out without the waiver or alteration.

Under 45 CFR 46.116(d), an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent otherwise required under 45 CFR part 46, or waive the requirements to obtain informed consent provided the IRB finds and documents that: (1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4)

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

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⁸⁴ 45 CFR 46.102(f).

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⁸⁷ 45 CFR part 160 and 45 CFR part 164, subparts A and D.

⁸⁸ The Common Rule evolved from a long series of measures designed to protect individual research subjects from physical and mental harm. In contrast, the HIPAA Privacy Rule evolved from data protection standards such as the Fair Information Practices. See Pritts JL (2008). *The Importance and Value of Protecting the Privacy of Health Information: The Roles of the HIPAA Privacy Rule and the Common Rule in Health Research*.

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[Docket No. USCG-2011-0615]

RIN 1625-AA00

Safety Zone; Fourth Annual Chillounge Night St. Petersburg Fireworks Display, Tampa Bay, St. Petersburg, FL

AGENCY: Coast Guard, DHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Coast Guard proposes to establish a temporary safety zone on the waters of Tampa Bay in St. Petersburg, Florida during the Fourth Annual Chillounge Night St. Petersburg Fireworks Display on Saturday, November 19, 2011. The safety zone is necessary to protect the public from the hazards associated with launching fireworks over navigable waters of the United States. Persons and vessels would be prohibited from entering, transiting through, anchoring in, or remaining within the safety zone unless authorized by the Captain of the Port St. Petersburg or a designated representative.

DATES: Comments and related material must be received by the Coast Guard on or before September 9, 2011. Requests for public meetings must be received by the Coast Guard on or before August 10, 2011.

ADDRESSES: You may submit comments identified by docket number USCG-2011-0615 using any one of the following methods:

(1) *Federal eRulemaking Portal:* <http://www.regulations.gov>.

(2) *Fax:* 202-493-2251.

(3) *Mail:* Docket Management Facility (M-30), U.S. Department of Transportation, West Building Ground Floor, Room W12-140, 1200 New Jersey Avenue, SE., Washington, DC 20590-0001.

(4) *Hand delivery:* Same as mail address above, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. The telephone number is 202-366-9329.

To avoid duplication, please use only one of these four methods. See the "Public Participation and Request for Comments" portion of the **SUPPLEMENTARY INFORMATION** section below for instructions on submitting comments.

FOR FURTHER INFORMATION CONTACT: If you have questions on this proposed rule, call or e-mail Marine Science Technician First Class Jo A. Hoover, Sector St. Petersburg Prevention Department, Coast Guard; telephone 813-228-2191, e-mail Jo.A.Hoover@uscg.mil. If you have questions on viewing or submitting material to the docket, call Renee V. Wright, Program Manager, Docket Operations, telephone 202-366-9826.

SUPPLEMENTARY INFORMATION:

Public Participation and Request for Comments

We encourage you to participate in this rulemaking by submitting comments and related materials. All comments received will be posted without change to <http://www.regulations.gov> and will include any personal information you have provided.

Submitting Comments

If you submit a comment, please include the docket number for this rulemaking (USCG-2011-0615), indicate the specific section of this document to which each comment applies, and provide a reason for each suggestion or recommendation. You may submit your comments and material online (via <http://www.regulations.gov>) or by fax, mail, or hand delivery, but please use only one of these means. If you submit a comment online via <http://www.regulations.gov>, it will be considered received by the Coast Guard when you successfully transmit the comment. If you fax, hand deliver, or mail your comment, it will be considered as having been received by the Coast Guard when it is received at the Docket Management Facility. We recommend that you include your name and a mailing address, an e-mail address, or a telephone number in the body of your document so that we can contact you if we have questions regarding your submission.

To submit your comment online, go to <http://www.regulations.gov>, click on the "submit a comment" box, which will

then become highlighted in blue. In the "Document Type" drop down menu select "Proposed Rule" and insert "USCG-2011-0615" in the "Keyword" box. Click "Search" then click on the balloon shape in the "Actions" column. If you submit your comments by mail or hand delivery, submit them in an unbound format, no larger than 8½ by 11 inches, suitable for copying and electronic filing. If you submit comments by mail and would like to know that they reached the Facility, please enclose a stamped, self-addressed postcard or envelope. We will consider all comments and material received during the comment period and may change the rule based on your comments.

Viewing Comments and Documents

To view comments, as well as documents mentioned in this preamble as being available in the docket, go to <http://www.regulations.gov>, click on the "read comments" box, which will then become highlighted in blue. In the "Keyword" box insert "USCG-2011-0615" and click "Search." Click the "Open Docket Folder" in the "Actions" column. You may also visit the Docket Management Facility in Room W12-140 on the ground floor of the Department of Transportation West Building, 1200 New Jersey Avenue, SE., Washington, DC 20590, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. We have an agreement with the Department of Transportation to use the Docket Management Facility.

Privacy Act

Anyone can search the electronic form of comments received into any of our dockets by the name of the individual submitting the comment (or signing the comment, if submitted on behalf of an association, business, labor union, etc.). You may review a Privacy Act notice regarding our public dockets in the January 17, 2008, issue of the **Federal Register** (73 FR 3316).

Public Meeting

We do not now plan to hold a public meeting. But you may submit a request for one on or before August 10, 2011 using one of the four methods specified under **ADDRESSES**. Please explain why you believe a public meeting would be beneficial. If we determine that one would aid this rulemaking, we will hold one at a time and place announced by a later notice in the **Federal Register**.

Basis and Purpose

The legal basis for the proposed rule is the Coast Guard's authority to establish regulated navigation areas and