Citizens for Responsible Care and Research, Inc. (CIRCARE)
(A wholly independent, volunteer, non-profit, tax-exempt organization,
incorporated under the laws of the State of New York)
1024 North 5th Street
Philadelphia, Pennsylvania 19123-1404
www.circare.org; web@circare.org
215.627.5335

September 21, 2011

Jerry Menikoff, M.D., J.D
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

In re: Docket No. HHS-OPHS–2011–0005,

> Advance Notice of Proposed Rulemaking, Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512 (2011),

This letter responds to the solicitation by the Office of the Secretary of the Department of Health and Human Services (HHS) in coordination with the Office of Science and Technology Policy for public comment on proposed rulemaking to amend human subjects protection regulations codified at 46 C.F.R. pts. 46, 160, and 164 and 21 C.F.R. pts. 50 and 56.

Citizens for Responsible Care and Research, Inc. (CIRCARE) is the oldest human research protection organization in the United States and is entirely independent. We advocate conscionable research. We are private citizens dedicated to effective protection of human subjects in behavioral and biomedical research. Our board members and officers are from science, law, research policy, ethics, medicine, nursing, social work, education, and care-giving. Some of have been voluntary subjects of research. Experience represented in our board and officers includes governmental and academic Institutional Review Board membership and chairmanship and university faculty in national and international law and ethics of human subjects research. We serve without pay. CIRCARE receives no support from industry or government.

We address: (A) whether there is need to amend human subjects regulations at this time; (B) sources of law and regulatory intent; (C) experience under current regulations; (D) topical sections and numbered questions in the ANPRM; and (E) general concerns in response to this Advance Notice of Proposed Rulemaking (ANPRM). Then, at (F), we follow these comments with a concluding, summary comment. An Appendix follows, with our submissions to the Presidential Commission on Bioethical Issues.

A. Whether there is need to amend human subjects regulations at this time.

We see no need to amend the human subjects regulations in the proposed manner at this time.

The ANPRM includes proposed changes that would require amendment because they would alter the Common Rule and its Food and Drug Administration implementation substantively. We conclude that, on the whole:

1. Many of the substantive changes proposed would weaken protections by minimizing or eliminating review and consent requirements and therefore are counter to statutory authority and intent.

2. The proposal would automatically dismiss large categories of possibly risky research as without regulatory significance. It thus does not reduce regulatory scrutiny to the actual level of risk but rather to the level that the agency chooses not to ignore. This approach is counter to statute.

3. By eliminating or minimizing consent and ethics review and by establishing data banks for use in "empiric" analysis, the proposal, counter to statute, would not substantively contribute to enforcement of human subjects protections but would foster massive invasions of privacy.

3. Important parts of the ANPRM rationale rely on inadequate information, which comes largely not from independent sources but from research agencies and institutions that are regulated; the ANPRM does not mention or deal with the analyses, conclusions, and recommendations in the Final Report of the (President's) Advisory Committee on Human Radiation Experiments, which emphasized the ethical importance of voluntary, informed consent in circumstances conducive to voluntariness and called for strengthening of protections for human subjects of research.

4. Many if not all of those proposed changes that are desirable can be accomplished with notice-and-comment guidance.

5. Serious human research protections problems identified by the Office of Inspector General (OIG) of the Department of Health and Human Services, by the Government Accountability Office (GAO), by the Advisory Committee on Human Radiation Experiments, and by the Food and Drug Administration (FDA) in numerous warning letters are unlikely to be remedied by the substantive changes proposed in this ANPRM and might be exacerbated by some of the ANPRM recommendations. These problems can be addressed constructively by:

(a) Institutional Review Board and investigator deference to the Belmont Principles in interpreting the Common Rule.

(b) Notice-and-comment guidance consistent with findings and conclusions by the OIG, GAO, and Advisory Committee on Human Radiation Experiments.

(c) Stronger will to enforce.

(d) Far more effort to foster willingness to comply.

6. The Common Rule and its regulatory intent are relatively simple. Many of the problems ascribed to the Common Rule inhere not in the rule itself but in research institutions' own bureaucratic practices and attempts to evade its plain intent.

7. We believe that these attempts to remove extensive areas of research from scrutiny for human subjects research protections and to foster massive acquisitions of personal information without informed consent will lead to increased distrust of research, researchers, and enforcement agencies and make it much more difficult to carry out meritorious research.

While some critics of the regulation complain about the financial cost of compliance, we note that an institutional human research protections program is a condition of federal funding, which includes allowance for overhead.

We recognize that Federal regulatory and research-funding entities are short of critically needed resources. But protection of human subjects would be weakened markedly by those major portions of the ANPRM that would rely on automaticity and on cutting back or eliminating consent and review requirements.

The ANPRM implies urgency and assumes that medicine, public health, and welfare may be set back unless protection of human subjects of research is curtailed as the ANPRM proposes. Research may or may not lead to dearly sought improvement in medical practice, health, and welfare. We are advocates for conscionable research. But we must beware the therapeutic misconception. Our comments are directed to protecting the human subjects of behavioral and biomedical research and not to the practice of medicine and the regular operation of health and welfare programs.

We emphasize the legal and ethical importance of informed consent—knowing, voluntary, in circumstances conducive to voluntariness and vindication of rights under law by persons aggrieved. To hold otherwise is to offend the inherent dignity of the individual person and to contravene long-standing law.

(B) Sources of law and regulatory intent.

The ANPRM rightly notes as a primary source of authority 42 U.S.C. § 289. It is important to note the statutory statement of intent (here underscored), at 42 U.S.C. § 289(a):

> Sec. 289. Institutional review boards; ethics guidance program
>
> (a) The Secretary shall by regulation require that each entity which applies for a grant, contract, or cooperative agreement under this chapter for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant, contract, or cooperative agreement assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an "Institutional Review Board") to review biomedical and behavioral research involving human subjects conducted at or supported by such entity in order to protect the rights of the human subjects of such research.

Accordingly, the implementing regulations and amendments thereof must be for the purpose of "protecting the rights of the human subjects" of biomedical and behavioral research.

The ANPRM rightly invokes the Belmont Report and its ethical principles of beneficence, justice, and respect for persons as a continuing statement of regulatory intent, implementing statutory intent.

We call your attention to other highly pertinent law as well, including these fundamental provisions:

> The right of the people to be secure in their persons, houses, papers, and effects, against unreasonable searches and seizures, shall not be violated . . . . U.S. Const. Amdt. IV.
>
> No person shall be . . . deprived of life, liberty, or property without due process of law . . . . U.S. Const. Amdt. V.
>
> . . . nor shall any state deprive any person of life, liberty, or property, without due process of law, nor deny to any person within its jurisdiction the equal protection of the laws. U.S. Const. Amdt. XIV.

. Relevant treaties into which the United States has entered are U.S. law, directly applicable.

The United States is a state party to the International Covenant on Civil and Political Rights, Done at New York December 16, 1966, entered into force March 23, 1976; for the United States September 8, 1992, T.I.A.S., 999 U.N.T.S. 171 (167 ratifications as of August 24, 2911), which provides in pertinent part:

> No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation. Int'l Covenant on Civil & Political Rights, art. 7 (emphasis added).

And:

> 1 . In time of public emergency which threatens the life of the nation and the existence of which is officially proclaimed, the States Parties to the present Covenant may take measures derogating from their obligations under the present Covenant to the extent strictly required by the exigencies of the situation . . . .
>
> 2. No derogation from articles 6, 7, 8 (paragraphs I and 2), 11, 15, 16 and 18 may be made under this provision. Int'l Covenant on Civil & Political Rights, art. 4 (emphasis added).

In other words, the bar to scientific and medical experimentation on human beings absent their informed consent is absolute. Exceptions to Article 7 are not allowed even in public emergency. (This does not prohibit use of experimental medical technique for the benefit of an individual patient in a life-threatening emergency if there is no alternative available; the FDA's emergency-research provision comports with these treaty provisions.)

In its initial report interpreting U.S. obligations and compliance under the International Covenant on Civil and Political Rights, the United States recognized that the prohibition of "medical or scientific experimentation" absent informed consent stands on its own, independent of the prohibition of torture and cruel, inhuman or degrading treatment or punishment, that the treaty applies to non-medical as well as medical research, that the treaty applies within the United States as well as to U.S. Government transnational activities, and that human subjects research without informed consent is Constitutionally prohibited:

> 178. Medical or scientific experimentation. Non-consensual experimentation is illegal in the U.S. Specifically, it would violate the Fourth Amendment's proscription against unreasonable searches and seizures (including seizing a person's body), the Fifth Amendment's proscription against depriving one of life, liberty or property without due process, and the Eighth Amendment's prohibition against the infliction of cruel and unusual punishment.

179. Comprehensive control of unapproved drugs is vested by statute in the federal Food and Drug Administration (FDA). The general use of such drugs is prohibited, see 21 .S.C. section 355(a), but the FDA permits their use in experimental research under certain conditions. 21 U.S.C. sections 355(i), 357(d); 21 C.F.R. section Part 50. The involvement of human beings in such research is prohibited unless the subject or the subject's legally authorized representative has provided informed consent, with the limited exceptions described below. The FDA regulations state in detail the elements of informed consent. 21 C.F.R. sections 50.41-50.48.

180. An exception is made where the human subject is confronted by a life-threatening situation requiring use of the test article, legally effective consent cannot be obtained from the subject, time precludes consent from the subject's legal representative, and there is no comparable alternative therapy available. The Commissioner of the FDA may also determine that obtaining consent is not necessary if the appropriate Department of Defense official certifies that informed consent is not feasible in a specific military operation involving combat or the immediate threat of combat. . . .

* * * * *

182. In December 1993, it became widely known that between 1944 and 1974 the United States Government conducted and sponsored a number of experiments involving exposure of humans to radiation. While certain experiments resulted in valuable medical advances including radiation treatment for cancer and the use of isotopes to diagnose illnesses, a number of the experiments may not have been conducted according to modern-day ethical guidelines. Moreover, the majority of the records of the experiments were kept secret for years. The United States Government has taken a number of steps to investigate the propriety of the experiments. . . . By executive order in January 1994, the President established the Advisory Committee on Human Radiation Experiments, which is charged with investigating the propriety and ethics of all human radiation experiments conducted by the Government, and determining whether researchers obtained informed consent from their subjects. . . ..

183. Experimentation on prisoners is restricted by the Fourth, Fifth, and Eighth Amendments to the United States Constitution, by statutes, and by agency rules and regulations promulgated in response to such provisions. As a general matter, in the United States, "[e]very human being of adult years or sound mind has a right to determine what shall be done with his own body ...". Schloendorff v. Society of New York Hospitals, 211 N.Y. 125, 105 N.E. 92, 93 (1914). Accordingly, prisoners are almost always free to consent to any regular medical or surgical procedure for treatment of their medical conditions. Consent must be informed": the inmate must

be informed of the risks of the treatment; must be made aware of alternatives to the treatment; and must be mentally competent to make the decision. But due to possible "coercive factors, some blatant and some subtle, in the prison milieu", (James J. Gobert and Neil P. Cohen, Rights of Prisoners, New York: McGraw Hill, Inc., 1981, pp. 350-51) prison regulations generally do not permit inmates to participate in medical and scientific research.

184. The Federal Bureau of Prisons prohibits medical experimentation or pharmaceutical testing of any type on all inmates in the custody of the Attorney General who are assigned to the Bureau of Prisons. 28 C.F.R. section 512.11(c).

185. Moreover, the federal government strictly regulates itself when conducting, funding, or regulating research in prison settings. An Institutional Review Board, which approves and oversees all research done in connection with the federal government, must have at least one prisoner or prisoner representative if prisoners are to be used as subjects in the study. Research involving prisoners must present no more than a minimal risk to the subject, and those risks must be similar to risks accepted by non-prisoner volunteers. See 28 C.F.R. Part 46. Furthermore, guidelines established by the Department of Health and Human Services provide that the research proposed must fall into one of four categories:

"(1) Study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the study presents no more than a minimal risk and no more than inconvenience to the subject;

(2) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subject;

(3) Research on conditions particularly affecting prisoners as a class;

(4) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the subject." 45 C.F.R. section 46.306(a)(2).

186. Similar standards have been developed within the broader correctional community that strictly limit the types of research conducted in prisons, even with an inmate's consent. For example, in its mandatory requirements for institutional accreditation, the American Correctional Association (ACA) stipulates that: "Written policy and practice prohibit the use of inmates for medical, pharmaceutical, or cosmetic experiments. This policy does not preclude individual treatment of an inmate based on his or her need for a specific medical procedure that is not generally available (emphasis added)."Mandatory Standard 3-4373, Section E,

> "Health Care", in Standards for Adult Correctional Institutions, 3rd ed., Laurel, Maryland: American Correctional Association, January 1990, p. 126. The commentary accompanying this mandatory regulation reads: "Experimental programmes include aversive conditioning, psychosurgery, and the application of cosmetic substances being tested prior to sale to the general public. An individual's treatment with a new medical procedure by his or her physician should be undertaken only after the inmate has received full explanation of the positive and negative features of the treatment." (Id.)
>
> 187. Non-medical, academic research on inmates is normally allowable in federal and state prisons with the inmate's express consent. This type of research normally consists of inmate interviews and surveys. Inmates are not required to participate in any research activities other than those conducted by correctional officials for purposes of inmate classification, designation, or ascertaining inmate programme needs (e.g., employment preparation, educational development, and substance abuse and family counselling).

U.S., Initial reports of States parties [to the International Covenant on Civil and Political Rights]due in 1993; United States of America (CCPR Human Rights Comm., State Party Report CCPR/C/81/Add.4, 1994), <http://www.unhchr.ch/tbs/doc.nsf/(Symbol)/da936c49ed8a9a8f8025655c005281cf> (last visited Aug. 24, 2011).

All U.S. Government departments and agencies long have been under Presidential order to implement the Covenant and other human rights treaties to which the United States is a state party. Exec. Order No.13,107, 63 WEEKLY COMP. PRES. DOC. 68,991 (Dec. 15, 1998).

Implementing legislation is not required. Constitutional scholarship has found Senate-imposed "non-self-executing" declarations in this context to be without legal significance. Louis Henkin, FOREIGN AFFAIRS AND THE CONSTITUTION (2d. ed. 1996) at 203. Louis Henkin, *U.S. Ratification of Human Rights Conventions: The Ghost of Senator Bricker,* 89 AM. J. INT'L L. 341-350 (1995). Unless they have renounced a treaty its signatories are obliged not to engage in conduct contrary to the treaty's principles and purposes. Vienna Convention on the Law of Treaties, Done at Vienna on 23 May 1969, entered into force on 27 January 1980, 1155 U.N.T.S. 331 (111 ratifications as of August 25, 2011), art. 18 <http://untreaty.un.org/ilc/texts/instruments/english/conventions/1_1_1969.pdf> (last visited August 25, 2011). The United States, which signed but has not yet ratified the Vienna Convention, long has recognized it nevertheless as codifying customary and therefore binding international law on treaty interpretation. President Richard M. Nixon, Letter of Submittal accompanying the Vienna Convention, Oct. 18, 1971, and U.S. Department of State analysis, *in* TREATIES AND OTHER INTERNATIONAL AGREEMENTS: THE ROLE OF THE UNITED STATES

SENATE, STUDY FOR THE COMM. ON FOREIGN RELATIONS, U.S. SENATE, BY THE CONG. RES. SERVICE, 103D CONG., 1ST SESS., S. PRT. 103-53 (COMM. PRINT 1993). *Accord* U.S. Department of State website, <http://www.state.gov/s/l/treaty/faqs/70139.htm> (last visited August 25, 2011). Treaties are to "be interpreted in good faith in accordance with the ordinary meaning" of their terms, Vienna Convention art. 31, and interpretation should not lead to a "manifestly absurd or unreasonable" result. Vienna Convention art. 32.

The International Covenant applies not only domestically but wherever its states party are engaged and whether or not humanitarian law and the laws of war also apply in the circumstances. Legal Consequences of the Construction of a Wall in the Occupied Palestinian Territory, Advisory Op., I.C.J., 9 July 2004, 43 I.L.M. 1009, <http://www.icj-cij.org/docket/files/131/1671.pdf> (last visited August 25, 2011). Geneva Conventions of 1949 (from common articles: for wounded and sick armed forces at sea or in the field: no biological experiments; for prisoners of war: no medical or scientific experiments not justified by the individual prisoner's medical need and conducted in this individual prisoner's interests).

Humanitarian law also restricts and in some cases bars research on human beings; the relevant law includes:

> Geneva Conventions of 1949 (from common articles: for wounded and sick armed forces at sea or in the field: no biological experiments; for prisoners of war: no medical or scientific experiments not justified by the individual prisoner's medical need and conducted in this individual prisoner's interests).
>
> Geneva Conventions Additional Protocols of 1977, concerning victims of armed conflicts (for wounded, sick, or shipwrecked persons: no medical or scientific experiments even with consent; for interned, detained, or otherwise held persons: no medical procedure not indicated by the individual's medical status; no medical procedure inconsistent with medical standards for free persons).

These are legal obligations of countries, not only of their military personnel.

Under the expanded International Health Regulations, implementation of public health measures and related research interventions "shall be with full respect for the dignity, human rights and fundamental freedoms of persons." World Health Organization: Revision of the International Health Regulations [May 23, 2005], 44 I.L.M. 2012 (2005), art. 3 ¶ 1.

U.S. agency-specific law restricts what might be allowable under the Common Rule alone. For example, educational systems and institutions that receive support from the U.S. Department of Education are subject to limitations on intrusive surveys and data disclosures: Family Educational Rights and Privacy Act, 20 U.S.C. §1232g; 34 C.F.R. pt. 99), and Protection of Pupil Rights Amendment, 20 U.S.C. §1232h; 34 CFR Part 98).

Additionally, within the United States, local probate, mental health, and family law control who may be a legally authorized representative for decisionally incapacitated and incompetent persons and may limit or bar consent powers. For example, in the District of Columbia a guardian shall not have the power to consent to "experimental treatment or research" "unless the power to consent is expressly set forth in the order of appointment or after subsequent hearing and order of the court." D.C. Code § 21-2047(c)(2).

In connection with the Common Rule's prohibition of exculpatory consent language the relevant law includes all of tort law—the intentional torts (e.g., battery) as well as negligence.

When the law says no, it means no.

(C) Experience under current regulations.

Responses of research entities, whether governmental or otherwise, and researchers to the Common Rule and its implementation by various federal agencies vary greatly in quality, i.e., in sincerity and effectiveness of effort to comply with the intent and letter of human subjects protection regulations. We have seen the same institutions behave well and poorly. Compliance lapses are failures of enforcement, not failures of the rule. The Common Rule as it stands is a clear, easily learned, and workable formulation. Many of the pressures for its revision stem not from problems in the rule but from institutional problems, insensitively to vulnerability, and resentment of regulation. Many of the criticisms seem to come from those who try to parse the rule finely enough to find safe harbor from its protective intent.

The theme that the human subjects regulations are overprotective recurs among many, but far from all, research program and human subjects protection administrators. The theme that the regulations are too inconvenient recurs even among some bioethicists, even some in government. The expression "regulatory burden" has been applied to human subjects protection recently not only by some research institutions' leaders but even in government. The research adduced in the ANPRM to support such criticisms consists almost entirely of opinion polling in the regulated community. Yet our experience, the nature and variety of research proposed or ongoing, and the Food and Drug Administration's steady flow of warning letters concerning violation of human subjects protection regulations confirm continuing need for strong protections—even in a regulated community that has a huge investment and long experience in the proper conduct of human subjects research.

Organization of human subjects protection programs (institutional responsibilities, under the Common Rule) also varies greatly. In practical effect, if not in formal organization, the leadership of research institutions sometimes delegates human subjects program responsibilities entirely to IRB's and their administrators. In formal organization as well as in practical effect the

institutional official for human subjects protection is the same individual who is responsible for bringing in research money. In formal organization and practical effect the Institutional Research Board (IRB) often is relegated to what operationally is a department of regulatory paperwork to satisfy the government. It is to adapt to this last and inadvisable model that much of the ANPRM seems to be directed—with its emphasis on qualifying definitions rather than on good-faith judgment and regulatory intent. Several IRB's conduct their business not by face-to-face meetings but by teleconference and electronic processing of documents in what amounts to editing rather than ethics review. In our experience, most IRB's, their administrators, and human subjects ethics training providers seem to be ignorant or dismissive of law other than the Common Rule. Institutional support for IRB's is often insufficient. We are aware of attempts to thwart human subjects ethics review, to intimidate IRB members and staff, and to retaliate for good-faith IRB service.

We are unaware of research on whether accreditation of human subjects protection programs is efficacious in terms of enhanced protection. We are aware of instances of gross violation of regulatory intent by some programs that have been accredited.

Against a background of meritorious research, we are aware also of the dark side. Among problems that have come to our attention: Reckless research; serious departures from standards of medical care; intimidation of subjects; regarding of human subjects as objects; serious invasions of privacy by behavioral scientists, for example in genetic cross-linking of tissue samples and psychiatric and law-enforcement records unbeknown to subjects; a court-appointed psychiatrist's proposal to study court-referred patients for which psychiatric findings must be reported to the court; renewed attempts to use foster children and children otherwise in public custody as subjects for behavioral and psychotropic drug studies; attempts to use dying and seriously ill patients as research subjects without their consent and for purposes other than their medical benefit; research exploitation of cognitively impaired persons without lawful consent; eliciting blanket consent from medical students for unspecified future studies; attempts to evade the requirement of individual informed consent, for example by claiming impracticality; bullying of parents who decline to agree to intrusive probes into their family dynamics and their children's behavior; focus groups in crime-prevention studies where confidentiality was promised but disclosures within the focus groups could expose subjects and their families and friends to violence and death; using persons in substance abuse therapy groups to scout for possible study recruits; orally surveying refugees in refugee centers while disregarding their entitlement to and need for privacy; tracking former prisoners without their fully informed consent; choosing study populations primarily because of their proximity rather than because of likely scientific validity; ethnic stereotyping in choice of study population; pushing criminal defendants into study groups; longitudinal following of Internet behavior of identified adolescents without their consent; data-mining, without consent, of records concerning identifiable individuals; longitudinal studies of persons who

understood that their information would be de-identified before use; human subjects research on medical practices long proven as quackery; advertising for biosamples for research when the biosamples in fact are for sale; IRB failure to assess risk; intimidation of IRB members; lack of institutional support for IRB work; ostensibly confidential political opinion surveys in countries where human rights are not enforced.

We recognize a long, noble medical ethical tradition of concern for the individual patient; this is reflected in the Common Rule. We see no such tradition of beneficence and non-maleficence in behavioral and social science research, for which the ANPRM would largely minimize or eliminate ethical review and consent.

(D) Topical proposals and numbered questions in the ANPRM.

(For clarity, ANPRM text and questions are in italics, and our response is in roman type.)

II. Ensuring Risk-Based Protections

* * * * *

[T]he 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. . . ."

Matching scrutiny, oversight, and safety monitoring to anticipated and experienced risk is the proper thrust of the current regulation and agency guidance. The Common Rule needs no amendment in this regard. The ANPRM proposal instead would automatically minimize or eliminate effective review on the basis of broad category of study method rather than actual inquiry into the research proposal, experience with the protocol, vulnerability of subjects, and why these subjects were selected for this intervention into their lives.

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 . . .

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.

Mandatory physical data security and information protection standards along the lines of the data-security method standards established under HIPAA are highly desirable but yet might be inadequate in view of developments in data-mining technology and use.

Physical data security should not be confused with security as related to permissible access to data.

The HIPAA and its implementing regulation allow so many exceptions—government administrative inquiry, billing, fund-raising, and law-enforcement, for examples—that the HIPAA permissible data access model cannot effectively protect subjects' confidentiality.

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.

HIPAA permissible-access standards lag behind increasing technical ability and commercial, research, and law-enforcement interest in data-mining.

The ANPRM ignores the Gramm-Leach-Bliley Act, Pub. L. No. 106-102 §§ 501-510, 15 U.S.C. §§ 6801-6809, which establishes consumer privacy rights and provides for federal and state regulation of the gathering, holding, and confidentiality of personal information by business entities, including insurance companies. Gramm-Leach-Bliley overlaps with but is not entirely consistent with HIPAA. SEE General Accounting Office, Financial Privacy: Status of State Actions on Gramm-Leach-Bliley Act's Privacy Actions, Rep. No. GAO-02-361 (April 12, 2002) http://www.gpo.gov/fdsys/pkg/GAOREPORTS-GAO-02-361/html/GAOREPORTS-GAO-02-361.htm GAO-02-361 (last visited Sept. 1, 2011).

Unlike HIPAA, Gramm-Leach-Bliley provides at least some minimal remedial recourse for aggrieved individuals. The enforcement machinery for HIPAA is indirect and so minimal in relation to the numbers of unlawful disclosures as to constitute an ineffective deterrent. SEE, e.g., Kevin Sack, *Medical Data Of Thousands Posted Online: Billing Vendor Handled Leaked Records,* N.Y. TIMES, Sept. 9, 2011, at A1. Neither HIPAA nor Gramm-Leach-Bliley offers adequate protection, but both are among points of law that have to be taken into account in addressing these issues.

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).

We understand that the term "exempt" wrongly implies that there is no need to check to ensure whether the Common Rule applies. But this problem is

curable by agency guidance, and the proposed change in terminology would sow confusion.

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.

This arrangement would leave prospective and actual subjects unprotected by a system that was supposed to have projects considered by individuals from different backgrounds.

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).

This arrangement could perpetuate ethically consequential error.

Elimination of continuing review would leave subjects unprotected where review might turn up problems in the protocol or might reveal that the reason for the research has been obviated.

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.

Risk often depends upon who is at risk in what circumstances. The ANPRM suggests no protective substitute for individualized inquiry for each research project.

The current information requirements are not onerous. Reducing the information submission requirement will make it more difficult for institutions, IRB's, and government program officers to spot problems.

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;

This approach leaves room for research without review and therefore is contrary to law.

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;

This approach leaves room for research without review and therefore is contrary to law.

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);

This approach fails to deal with research that would continue to be covered by U.S. Department of Education Regulations, with research for which informed consent was never sought or was defective, and with research that is unethically and possibly illegally intrusive.

The data security and information protection standards proposed by the ANPRM are inadequate.

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);

Here again, this approach fails to deal with research that would continue to be covered by U.S. Department of Education Regulations, with research for which informed consent was never sought or was defective, and with research that is unethically and possibly illegally intrusive.

Here again, the data security and information protection standards proposed by the ANPRM are inadequate.

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.

The anticipated new consent requirements are far from adequate. This proposal weakens protections and could violate terms of consent given when the specimens were collected.

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);

This proposal raises serious risk of exposure of individuals to invasion of their privacy without their knowledge or consent.

and

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

Human subjects protection audits of primary and secondary biospecimens data access and use are essential, whether or not the ANPRM proposals take effect and are an inherently governmental function.

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.

This proposal is contrary to law in that it would not protect but rather would operate against the rights of subjects by eliminating actually informed consent and would eliminate ethical review of biospecimen collection, use, and circumstances of consent.

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.

The ANPRM analysis reflects no awareness of serious problems that we have seen in some behavioral and social research. See our comments above at (C) Experience under current regulations.

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. [Note omitted.]

We agree that unwanted disclosure entails substantial risk. We disagree that disclosure is the only informational risk. The getting of the information and the linking of information can entail substantial risk—especially that of invasion of privacy. Against the risk of invasion of privacy, the ANPRM's proposed design is deficient and, contrary to law, increases risk.

We agree that inadequate data security is a major problem. We disagree that it is a one-dimensional, protect-the-data issue. Data security questions also include those of authorized access and vindication of privacy rights.

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. [Note omitted.]

Furthermore, review of informational risk is an inefficient use of an IRB's time.

We disagree. Review for human subjects research ethics—including not only risk but also subject selection, vulnerability, and content and circumstances

of informed consent—is an IRB duty, whether the research intervention is biomedical or otherwise.

The ANPRM analysis of informational risk is insufficient; it deals only with the information gained, undifferentiated as to hazards that disclosure would pose for individuals vulnerable to the consequences of disclosure.

The ANPRM states that the primary risk from most behavioral and social science is "informational," in the sense of unwanted disclosure. The ANPRM drafters conclude that data standards can minimize or all but eliminate such risk and that therefore most behavioral and social research is "minimal risk, " so the ethics of the research need not be reviewed fully and regularly and might even be conducted without informed consent. But the ANPRM statements here are neither accurate nor dispositive.

The IRB duty to assess risk requires not only assessing the likelihood of untoward consequences of research but also assessing the research intervention itself. The ANPRM drafters rightly recognize that unwanted disclosure is a problem. But they fail to recognize that how the information is acquired may be troubling also.

The ANPRM would cut back severely the ability of reviewers to protect subjects from research activities that involve wrongful, actionable conduct, especially the privacy and defamation torts. Each represents "an interference with the right of the plaintiff . . . 'to be let alone'": Intrusion upon the plaintiff's seclusion or solitude, or into his or her private affairs (i.e., invasion of privacy); public disclosure (to any public, no matter how small) of embarrassing private facts; placing the plaintiff publicly in a false light; and appropriation, for the defendant's advantage, of the plaintiff's name or likeness. William L. Prosser, *Privacy,* 48 CAL. L. REV. 383, 388-89 (1960).

Standardized data protections, rather than IRB review, may be a more effective way to minimize informational risks.

It may be argued that IRB's do not adequately protect research recruits and research subjects now in these regards. We believe that is so. But we solution lies not in weakening the regulations but in strengthening the will to comply and the will to enforce.

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. . . .

As noted above, the HIPAA permissible-access standards are unprotective and are not apposite to much of the problem posed by inadequately reviewed, inadequately overseen research..

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.

The ANPRM proposes that HIPAA permissible-access standards substitute for IRB assessment. But vulnerability and intrusiveness enter the picture. We do not understand how if "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

. . . 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.

As we point out elsewhere in our response, the data security and information protection standards proposed in this ANPRM are far from sufficient.

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. . . .

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. . . .

While we agree that follow-up may be medically and scientifically important, we are aware of follow-up efforts that amount to invasion of privacy, with skip-tracing techniques that increase the informational vulnerability of subjects. Continuing review should not be abolished in any category.

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 . . . and is found by the reviewer(s) to involve no more than minimal risk. . . .

(a) Eligibility for Expedited Review

. . . 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 . . . review and update the list, based on a systematic, empirical assessment of the levels of risk. . . .

The proposed mechanism is questionable. A standing federal panel would lack transparency. An advisory committee likely would be drawn largely from the regulated community and advocacy committees. OHRP and FDA have another, more open mechanism available: Use of the Negotiated Rulemaking Act, 5 U.S.C. §§ 561 et seq., which requires, transparency, membership balance, and facilitation and convening by a neutral.

Reliance on "systematic, empirical assessment" is ill-conceived. It would substitute statistical analysis of aggregated data for inquiry into individual cases of how data are collected as well as how data are protected.

This would provide greater clarity about what would beconsidered to constitute minimal risk . . . .,

We disagree, for the reason stated immediately above.

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

. . . Yet many studies . . . — particularly those in the social and behavioral field—are frequently required to undergo review by a convened IRB. [Note omitted.] *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.

The non-trivial possibility of invasion of privacy means that the proposed default presumption would weaken existing protections.

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

* * * * *

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.

All current criteria should be retained. To remove any of these criteria weakens the Common Rule and, contrary to law, fails to respect the rights of human subjects of behavioral, social, and biomedical research.

All of these criteria together long have constituted a reasonably stable, predictable set of regulatory standards. We do not see how stability, predictability, and adequate consistency of decision, both within and among research institutions, can be enhanced by eliminating or substantially weakening standards for decision.

To weaken or remove any or all of these criteria not only would curtail protection for human subjects of research. It would leave researchers facing the prospect of arbitrary IRB decisionmaking, and it would substantially increase the liability of exposure of researchers and research institutions for research interventions cleared by IRB's that operate without coherent, protective decisional criteria.

(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.

We disagree with the premises that studies labeled as "no more than minimal risk" are always correctly labeled and that the law lessens IRB responsibilities for certain types of research

Accordingly, we are considering changing the default to require no continuing review for studies that qualify for expedited review.

This proposal would leave research subjects unprotected and would disempower the IRB from ability to reconsider its analyses.

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.

This is meaningless without continuing review.

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.

This gives primary reviewers a great deal of power and deprives research subjects of the benefit of review from more than one perspective.

(c) Streamlining Documentation Requirements for Expedited Studies

. . . Although it is important to document why research qualifies for expedited review, it is unclear whether the time and effort expended in such preparation activities result in increased benefit in terms of protecting subjects.

The IRB must have an adequate basis for threshold decisions.

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. . . .

Risk should be assessed not only on the basis of the nature of the activity but also on the basis of subjects' vulnerability and the extent of voluntariness.

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

See above comments on proposals, and see responses to specific questions, below.

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?

The statutory mandate is to protect human subjects. Belmont cautions against exploiting the vulnerability and proximity of research subjects for

convenience of researchers. In this light, the Common Rule definition of "minimal risk" long has been confusing. When read apart from statutory authority and Belmont the current definition has sometimes been used to support inadequately reviewed behavioral, social, and biomedical research interventions into the daily lives of persons whose personal or social circumstances are far more stressful or disadvantaged than those of others for whom such interventions might actually be of little hazard. The extent and nature of risk to be borne by some research subjects is sometimes believed to justify less research protection because the subjects' health status, socioeconomic circumstances, education status, mental status, and/or legal status are normally low anyway. But the purpose of the rule with respect to "minimal risk" is to allow for reasoned judgment that certain proposed or ongoing research is too innocuous to warrant greater scrutiny. Its purpose is not to suggest that persons who are more heavily burdened deserve less research protection.

The ANPRM addresses the "minimal risk" definition problem one-dimensionally, proposing to reduce or effectively eliminate ethical review and even informed consent for certain categories of research activities. However, the degree and nature of hazard must be assessed also in terms of vulnerability of the prospective and actual research subjects. A categorical decision that a research activity is by its nature always "minimal risk" does not satisfy the law's protective requirement. For examples: Unwanted disclosure of personal information might be far more dangerous to some subjects than to others; a subject's circumstances or surrounding social circumstances might not be conducive to voluntary, informed decision.

As it stands, the definition is an inadequate protection but curable by agency guidance to this effect: A decision on whether a research activity is "minimal risk" must take into account not only the extent and nature of the research activity but also the vulnerability of the proposed and actual research subjects. A decision that a research activity is "minimal risk" cannot be one that results in lesser protections for the prospective and actual research subjects because of burdens of status and circumstance that they already bear normally. Put another way: A decision that a research activity is "minimal risk" should not depend on the subject's status and circumstances. The determination of "minimal risk" thus must take into account the specifics of the research proposal if it is to be legally and ethically sustainable. That can't be done automatically.

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?

No. The frequency and intensity of continuing review should not be reduced. A decision that a project qualifies for expedited review or is "minimal risk" should not stand without subsequent scrutiny. The ANPRM proposal to reduce or eliminate further review could perpetuate serious problems and give a

free pass to research activities that might be found highly dubious in adequate inquiry and review.

What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?

All human subjects research should undergo continuing review at least annually and more frequently as warranted by the nature of the research, the research population, concerns of IRB members, and concerns brought to the IRB's attention.

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 . . . ?

Yes, at least annually and more frequently if warranted by initially anticipated and subsequently experienced risk. Continuing oversight is essential to ensure promptness of data analysis, to ensure reporting of adverse events (including delayed events), to ensure that subjects are notified of results that might concern them, and to ensure that any proposed follow-up found to be necessary is conducted with respect for the rights of subjects.

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

No. IRB inquiry into the specific project under review is essential. The term "reasonably foreseeable" is a tort law fiction that depends upon inference by reference to a hypothetical "reasonable person" similarly situated. Would this be a hypothetical, similarly situated IRB member? If so the rule's essential requirement for non-scientist, non-affiliated, and non-conflicted members would be left meaningless. If a hypothetical, similarly situated researcher? Then the IRB's work would be left meaningless.

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?

We see no protective substitute for an individualized IRB inquiry that asks why and how this intervention into the lives of this particular study population is proposed. Question 5 seems to assume that invasion of privacy, for example, should not concern an IRB.

Question 6: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk?

This question assumes that it is possible a priori to decide that certain survey instruments and types of questions are minimal risk. But the analysis has to take into account who the research subjects are and what problems they face. Thus a political preference survey or even an education assessment could land a candid responder in jail in some countries. A standard sex-behavior survey could trigger serious problems in a child who has been abused.

How should the characteristics of the study population (e.g. mental health patients) be taken into consideration in the risk assessment?

Characteristics of all study population should be taken into account in assessing the lawfulness and voluntariness of consent, whether circumstances are conducive to voluntariness, whether circumstances are conducive to withdrawal of consent, whether confidentiality can be ensured, whether this particular population is exposed to distinctive risks and hazards (i.e., unwanted disclosures that could trigger violent reprisals), and whether consent would expose subjects to intrusions and/or risks and hazards later on.

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?

None.

Should any of the existing activities on that list be removed or revised?

No.

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.*

No. These are not tests normally performed in well-person medical examinations. They are invasive medical procedures, some of them more invasive, and they can have adverse clinical consequences. Usually they are performed only with the patient's informed consent. To suggest that they can be done without ensuring voluntariness is to put researchers and their employers at risk of liability for battery. To categorize them as minimal risk and therefore minimize review is contrary to statutory intent.

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?

No. This issue requires expert medical judgment in light of the circumstances and who the subjects are.

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?

The list should not be frozen. OHRP should be able to take items off the list if events warrant but should use negotiated rulemaking for additions to the list, perhaps every two years.

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?

All 45 C.F.R. 46.111 IRB-approval criteria should apply to all research covered by the Common Rule. To suggest less protection is contrary to statutory intent.

Question 11: What are the advantages of requiring that expedited review be conducted by an IRB member?

The IRB is responsible for review, expedited or not. The IRB may designate a primary reviewer, who should report findings to the full IRB, and IRB members should be able to question the primary reviewer and examine all related documents.

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?

No.

If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review?

Conflicts of interest. Lack of neutral outlook.

If so, what would qualify as being ''appropriately trained''?

Most of the IRB training that we have seen misstates or ignores highly relevant law.

Would the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?

Such changes would be at the cost of protection of subjects and would leave investigators vulnerable to arbitrary decisions because of the lack of ethics analysis from multiple viewpoints.

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?

Good-faith deference to the Belmont principles in interpreting the Common Rule would be an efficacious substitute for elaborate efforts to evade regulatory intent.

We do not believe that elaborate paperwork is an adequate substitute for a good-faith deliberative IRB process.

Are there specific elements that can be appropriately eliminated from protocols or consent forms?

No.

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?

Many of the criticisms leveled at IRB's involve conduct that stems not from the Common Rule but from causes that include: Bureaucracy superimposed by university administrations; from confusion of roles because the same people may be administrators of more than one regulatory entity within the university (example, at a major university: the IRB administrator's calling an investigator on a research integrity matter and saying, "This is the IRB"); IRB substitution of paperwork for face-to-face discussion with investigators; IRB substitution of electronic exchange of edits for face-to-face deliberations.

What entity or organization should developand disseminate such standardized document formats?

For its own purposes the National Institutes of Health developed several resources on human subjects protections. These are not uniformly applicable, but they suggest what can be useful. We note, for example, PROTOMECHANICS, the NIH Clinical Center guide to preparation of protocols. Much of this material had been available via `www.nih.gov` but has been removed—contravening White House Open Government directives.

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?

As we urge elsewhere in this response, the Administrative Procedure Act standard, a reasoned decision on the record, is an excellent model for IRB decisions. It can be as simple as an explanatory annotation on the record of decision. It needs no special form. OHRP and other research agencies should be checking these documents. Another form for this purpose would increase IRB and OHRP workload while providing no enforcement benefits.

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?

Yes, but not on a new form. OHRP can refer to the reasoned decisions on the record.

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?

Again, the Administrative Procedure Act standard is an excellent model: A reasoned decision on the record. No special report should be necessary.

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, . . .

The proposal would lessen current protections.

The data security and information protection standards described in the ANPRM do not address circumstances of data collection or circumstances of data access and use.

. . . and in some cases, informed consent would be required . . . .

Informed consent is required by law.

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 . . . .

The proposed change in terminology is confusing and unnecessary. Guidance can clarify that "exempt" for purposes of the Common Rule does not mean that the applicability of the rule need not be determined.

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.

Again, the data security and information protection standards proposed in the ANPRM are not adequately protective, nor do they increase protections for research subjects.

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 sothat they are clear enough that researchers could readily determine whether a study qualified to be in these categories.

Research subjects are not protected by a system that allows researchers to determine, without case-by-case check, whether they must comply with human subjects protection requirements.

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.

This proposal removes important protections from the Common Rule. The ANPRM posits unwarranted assumptions that because an adult is legally competent and the research intervention is not medically invasive a research subject is not vulnerable, that circumstances are conducive to voluntariness, that fully informed consent is unnecessary, and that the proposed data security standards are in themselves all the protection that is needed. This proposal is contrary to statutory intent.

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.

We disagree. We have seen defective proxy consents.

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. . . .

Riskiness of a study poses minimal risk depends not only on the kind of intervention but also on the individual subject's vulnerability, on the circumstances of decision to decline or consent, and on nature and circumstances of the intervention.

3. Limitations specified in the current exempt category 4 (research involving the use of existing information or biospecimens) 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 equirements would be imposed on some of these studies. (See Table 1 at the end of Section V for a summary of this proposal.)

This proposal would eliminate ethics review and expose individuals to open-ended intrusions into their privacy, without their consent, and could run counter to previous understandings concerning use of their biospecimens.

(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.

The proposed audit mechanism effectively removes large categories of research from neutral analysis to ascertain the ethicality of the research intervention in the particular circumstances. In disregard of the statutory requirement of IRB review, this proposal substitutes researcher a simple form and clerical processing. This proposal is counter to law.

The data security and information protection standards and proposed limited consent requirements are insufficient to provide reasonable assurance that the research satisfies the Common Rule.

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. . . . Key to this would be a requirement that researchers register their study with an institutional office by completing a brief form. . . . 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.

Again, this proposed mechanism would remove large categories of research from threshold neutral analysis to ascertain the ethicality of the research intervention in the particular circumstances. In disregard of the statutory requirement of IRB review, this proposal substitutes researcher a simple form and clerical processing.

This proposal establishes additional bureaucracy although IRB responsibility continues under the statute. The ANPRM statement goes yet farther, signaling that IRB review of research in these categories would be

"exceptionally rare." This statement invites lack of public confidence in human research protections and may redound to the detriment of human subjects researchers as well as human subjects themselves.

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.

This proposed policy removes a considerable amount of research from the protection intended by statute and may cause far more trouble than it seeks to prevent. Moreover, the cutback of the IRB mechanism would increase institutional and researcher liability exposure.

(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.

Again, riskiness of a study poses minimal risk depends not only on the kind of intervention but also on the individual subject's vulnerability, on the circumstances of decision to decline or consent, and on nature and circumstances of the intervention. Therefore ethical precautions regarding content and circumstances of decision to decline or consent should not be minimized.

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. . . .

We agree that written consent should be required but not in the general and open-ended way proposed in the ANPRM.

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.

Because of gaps in HIPAA and because of the possibilities of re-identification and cross-linking, these measures are insufficiently protective.

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

We concur on this point.

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.

We concur on this point.

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).

We disagree with this approach, inasmuch as the circumstances in which such consents are sought are not necessarily conducive to voluntariness and adequate understanding of the ramifications of such open-ended, irrevocable consent.

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.

This prohibition does not require regulatory amendment. It should be made clear in agency guidance, which should apply also to open-ended biospecimens research consent in connection public-benefit and entitlement programs.

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.

We discuss the Table 1 arrangement below. It is unprotective, does not satisfy legal minima, and exposes subjects to more informational hazard.

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.

These changes should not be applied, because there is no ethical review of the circumstances and content of consent.

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.

Does this proposal concern a subject's waiver of the right to decline or consent? Failure to permit an individual the choice of consenting or declining to be a research subject is contrary to law.

(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. . . .

The proposed changes thus would contravene statutory intent.

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?

No. They lessen or eliminate protections, including IRB review, and thus are contrary to law.

Would these changes be likely to discourage individuals from participating in research?

Yes. Prospective and continuing subjects could not be assured of credible measures to protect their rights in connection with this research. Further, the idea that some researchers and government agencies seek to reduce protective measures is likely to lead to a crisis of confidence in all human subjects research and in agencies responsible for enforcing human subjects protections. Conscientious researchers and important studies would be tarred by this broad brush. The consequent damage to meritorious research may be incalculable.

Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?

Yes. These proposals treat prospective and continuing tissue donors and subjects of behavioral and social research as objects, not as individuals. They invite the uninformed, possibly involuntary surrender of rights. They reduce or eliminate ethics review. They dismiss the possibility that privacy might be invaded unlawfully and unethically. They dismiss the possibility that behavioral and social research in some instances might place the subject in danger. They dismiss consent as unimportant, because they reflect no realization that an offense to individual dignity is as ethically problematic as an unwarrantedly dangerous medical experiment. They demonstrate ignorance of or contempt for law that mandates informed consent and IRB protection for subjects of behavioral and social research as well as subjects of biomedical research.

Question 15: Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category?

No. Nor should the expansions proposed here be accepted.

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?

Yes. The proposal is an unlawful carve-out, contrary to law, of most behavioral and social research and tissue donations from ethical and regulatory scrutiny.

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?. . .

No. The rights of human subjects are independent of the topic of the research.

Question 17: What specific social and behavioral research methodologies should fall within the Excused category?

None, for reasons stated above.

Under what circumstances, if any, should a study qualify for the Excused category if the study involves a form of deception . . .

None, for reasons stated above and because deception research is legally impermissible except where it is otherwise justifiable scientifically and ethically and the subject knows that there will be a deception and agrees to it.

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?

This question points up more of the troubling aspects of the Excused category, which militates against medical beneficence. Research subjects are entitled to their clinical data.

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?).

No. The default position must be that patients and research subjects are entitled to the data that concerns them. But deciding what data is clinically interpretable or clinically significant is not always practical, because clinicians differ and may change their minds on the basis of newly significant data.

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?

Researchers and research institutions proceed at their legal peril without adequate ethical review.

Question 20: The term ''Excused'' may not be the ideal term. . . . We welcome other suggestions for alternative labels that might be more appropriate.

As we state above, retain current terminology and explain it in guidance.

As proposed in this ANPRM, the term "Excused" describes an entirely different regulatory procedure, which is contrary to law.

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?

Yes, whether or not the "Excused" category is used. Compliance audits in our view are legally permissible because the regulation vests the research institution with responsibility to main a human subjects protection program (of which the IRB is one part) and because federal research funding generally includes provision for overhead. We know of nothing that precludes OHRP from compliance audits, and we note that FDA long has used compliance audits.

We caution that audits of paperwork (and its electronic equivalent) alone are insufficient and that audits should be extended to assess whether the institution and IRB attempt in good faith to comply with the letter and spirit of the law. This necessitates looking at how human protection programs operate and at how IRB's have reached their decisions.

Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements?

No. This is an agency task, which should be conducted as situations appear to warrant.

Should some other method besides a random selection be used to determine which Excused studies would be audited?

Systematic and random checking by cognizant Federal agencies.

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?

No. This proposal is no substitute for individualized review.

Might this new audit mechanism end up producing a greater burden than the current system?

Yes. As proposed, it establishes more bureaucracy and raises more questions in the absence of what would have been relatively straightforward ethical review.

Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category?

No. That's why the law establishes the IRB system and requires ethical review.

By allowing researchers to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened?

Yes, as we have explained above. The proposed process would eliminate the independent, neutral review that the law requires in order to protect human subjects of research.

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?

The question is unclear: Generally acceptable to whom? This proposed expansion is contrary to law.

And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

No.

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?

If all of the following conditions are satisfied: Specimens and data were obtained with informed consent in circumstances conducive to voluntariness; specimens and data are no longer identifiable and cannot be re-identified; specimens and data will not be used or otherwise made available for cross-linking studies that could lead to re-identification or to identifiability; and strong enforcement mechanisms are in place to guard against violations and provide for individual remedy.

Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes?

Informed consent to research is a legally required pre-condition to human subjects research.

Should a request to waive informed consent trigger a requirement for IRB review?

Yes. The burden should be on the investigator to provide that the specimens and data in question are not identifiable and cannot be made identifiable, and then the IRB should ascertain that the study is otherwise justifiable and that the conditions that we suggest above are satisfied.

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. Notes omitted.] . . . *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?*

Guidance should make clear that there is a rebuttable presumption that the work is research if the investigator is doing the work on a research budget, a research grant, a research contract, or a cooperative research agreement, or if results are to be presented or published in a research forum, or if the work is done as part of a research program.

The question of human subjects protocols for training researchers arises also. Guidance can make clear that these activities are research under the Common Rule. They entail direct or indirect interactions with human subjects and early steps in the question for "generalizable knowledge."

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?

No, for reasons that we state above.

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 valuation'')?

The default position should be full IRB review and informed consent.

Again, guidance should make clear that there is a rebuttable presumption that the work is research if the investigator is doing the work on a research budget, a research grant, a research contract, or a cooperative research agreement, or if results are to be presented or published in a research forum, or if the work is done as part of a research program.

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?

The statute applies to biomedical and behavioral research, and broader law applies the requirement of informed consent to all scientific and medical experimentation.

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)) . . . ?

The concept of a regulatorily consequential distinction between research and health care operations is useful and important. However, the HIPAA definitions are so woven into an already problematic regulatory arrangement that it cannot be applied directly.

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?. . .

Constitutionally the Common Rule must not inhibit freedom of the press or freedom of expression.

Here again, we suggest that if the question arises the OHRP and IRB follow this rule of thumb: There is a rebuttable presumption that the work is research if the investigator is doing the work on a research budget, a research grant, a research contract, or a cooperative research agreement, or if results are to be presented or published in a research forum, or if the work is done as part of a research program. These criteria should come into play if a project is proposed as exempt because it is a public health measure.

Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?

No. Guidance can clarify this, based on specific examples.

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?

We encounter misunderstanding of what such programs are.

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?

By new and improved agency guidance, which should make clear that the exemption applies to these narrowly defined projects only and not to various studies that investigators might wish to piggy-back onto them.

Would broadening the interpretation of the exemption result in inappropriately increased risks to participants in research?

Yes.

If so, how could such risks be mitigated?

By not expanding the kinds of research for which review is minimized or eliminated.

Also, is there a need to update or otherwise revise the ''OPRR Guidance on 45 CFR 46.101(b)(5)''?

Yes.

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? [Note omitted.] *If that is not how the provision is typically interpreted, is there a need to clarify its meaning?*

This question conflates two easily distinguished issues: Whether IRB's realize that as the law intends they are to evaluate impacts on and interactions with human subjects, including dignity interests, and whether IRB's realize that their task does not include evaluation of possible societal impacts (i.e., they are not charged with technology assessment). These issues can be clarified by agency guidance.

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). . . . Should the Common Rule

include a requirement that every institution must provide an appropriate appeal mechanism?

No. The Common Rule, properly, does not allow appeal of an IRB denial. The notion that there should be an appeal from an IRB denial misperceives the nature of the IRB task. The IRB's job is not to adjudicate between investigator and subject; rather it is to protect prospective and actual subjects and to ascertain whether the project proposal or protocol satisfies ethical standards and legal requirements for protection of human subjects. IRB proceedings are not adversary proceedings. Prospective and actual human subjects typically have no access to the proceedings and are not represented. The institutional official has the opportunity to say no when the IRB has said yes but cannot reverse an IRB's denial. Under the Common Rule, the Government can say no but cannot reverse a denial. This is as it should be, whether IRB proceedings are secretive (as they are typically) or not. To have it otherwise would intimidate IRB's and leave a system completely stacked against research subjects.

If so, what should be considered acceptable appeal mechanisms?

None. If investigators don't like the way an IRB works, they can complain to their institutional official, who can try to ascertain whether the IRB is doing its work and earning its Government trust.

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?

No. If investigators don't like the way an IRB works, they can complain to their institutional official, who can try to ascertain whether the IRB is doing the work entrusted to it by the Government.

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?

As we suggest at several points in this response, each IRB decision should be a reasoned decision on the record, the Administrative Procedure Act standard.

The institution is responsible for maintaining a program to protect human subjects. The program should not be delegated entirely to the IRB or to the IRB and its administrator(s). How threshold decisions are made is for the institution

to decide. However, the IRB has a broad responsibility to ensure that research subject IRB jurisdiction is overseen by the IRB.

The ANPRM seems to suggest an opportunity for intra-institution forum-shopping in this regard. This is hardly protective of research subjects.

III. Streamlining IRB Review of Multi-Site Studies

* * * * *

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?

Ultimately the research institution and research performer are liable for injury and must retain control over their own liability exposure. Neither OHRP nor FDA have legal authority to force a research entity to defer to an outside IRB, and prudent management would not do so without arrangements for indemnification.

If a central IRB for multi-site studies has a greater capacity for expert risk analysis, then an institution may see an advantage in deferring to a central IRB. But central IRB's must be independent and credible. The credibility of several commercial IRB's has been questioned for good reason, and the credibility of government central IRB's is subject to criticism for lack of true independence.

The disadvantages are, currently, a lack of independence, transparency, membership balance, accountability, and local knowledge on the part of central IRB's. Whether and how a central IRB's approval might be reversible by an institutional official is unclear.

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies?

Local IRB's are supposed to be familiar with the circumstances of their local study populations.

How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects?

Central IRB's typically lack independence, transparency, membership balance, accountability, and local knowledge.

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?

Yes, particularly as relates to knowledge of local conditions and the circumstances of the study population.

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?

Perhaps liability concerns do not affect institutional decisions as much as they should in this regard. If they did, institutions might take more care. These decisions too often may be made by the local IRB or its administrator. But these are institutional responsibilities, and it is up to the institution to govern its own liability exposure and to delegate IRB authority as appropriate to the minimization of research hazard and the protection of research subjects.

Would the changes we are considering adequately address these concerns?

No.

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

We have seen one local IRB discover a serious problem, relating to ostensibly confidential but self-incriminating admissions to law enforcement, that had been missed entirely by all other IRB's in a multi-site study.

We have also seen local IRB's that lack expertise required to review a protocol and assess risk for a multi-site study.

We are aware of central IRB refusal to recognize local concerns for inadequacy of consent documents.

Question 34: If there were only one IRB of record for multi-site studies, how should the IRB of record be selected?

By institutional representatives who have negotiating authority for this purpose, and in combination with basic plans for safety monitoring and agreement on relationships between the IRB and data and safety monitoring entity. The selected IRB of record should be able to call upon the requisite expertise and should not lack independence, transparency, membership balance, accountability, or capacity to ascertain local conditions and vulnerabilities. It should be free of conflicts of interest—whether financial or by association.

How could inappropriate forms of ''IRB shopping''—intentionally selecting an IRB that is likely to approve the study without proper scrutiny—be prevented?

"IRB shopping" can be deterred by a combination of enforcement techniques, including: Registration of submitted protocols and modifications; audits; stings, which have been very good sensitizers; opening IRB decision records to public view except for redaction of trade secrets; opening enforcement records to public access; opening assurances to public access.

Investigators and sponsors found to have "IRB shopped," that is, to have taken a protocol in one version or another to more than one IRB in order to get a favorable ruling, should be debarred. OHRP should audit IRB's for indications of lack of critical review and should take remedial action as appropriate.

We believe that as IRB operations and enforcement records are opened to public view, liability insurance carriers will be interested in pressuring their clients into operating their research protection programs properly.

IV. Improving Informed Consent

* * * * *

A. Improving Consent Forms

* * * * *

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

Primary contributing factors: Lack of consideration for the reader, and writing of consent forms in order to mislead and/or to intimidate the reader in order to protect institutional and sponsor interests; poor training; tendency to rely on old forms that others have used; institutional and sponsor insistence on highly questionable, defensive boilerplate.

These problems might be addressed by guidance and training that emphasize good-faith compliance and make clear the IRB's authority to reject institutional and sponsor defensive boilerplate.

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?

The problems mentioned here are covered already in the Common Rule. What is required is a combination of guidance and agency enforcement.

What modifications or deletions to the required elements would be appropriate?

None. Modifying or deleting any of the required elements would substantially weaken existing protections, contrary to statutory intent.

Question 37: Would the contemplated modifications improve the quality of consent forms?. . .

The ANPRM provides no specific information on the contemplated modifications.

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?

Guidance can urge the use of independent consent auditors where questions of vulnerability and/or involuntariness might arise.

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?

Weakening Common Rule protections as proposed in this ANPRM would raise questions of compatibility with HIPAA law, Gramm-Leach-Bliley Act law and policy, international law binding on the United States, International Conferences on Harmonization guidelines insofar as they have been given legal effect, and long-standing, widely embraced professional statements on the ethics of human subjects research.

Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required?

IRB's would be well-advised in guidance to provide for neutral consent auditors where subject vulnerability and circumstances are in question.

For example, should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?

Yes. Investigators should be required to disclose all relationship that a reasonable person would find material to a decision on whether to volunteer as a research subject.

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

* * * * *

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

The current regulation's allowance for research without informed consent should be removed. It is inconsistent with law. Scientific research on a human subject without informed consent is unlawful under the International Covenant on Civil and Political Rights unless the research is for the individual's benefit in a life-threatening emergency and there is no readily available medical alternative.

Question 42: In circumstances where the regulations would permit oral consent, what information should investigators be required to provide to prospective subjects?

All of the elements of informed consent currently required are essential to a knowing, voluntary decision in circumstances conducive to voluntariness.

Where oral consent procedures are used, there should be consent auditing and the making of a record by a qualified, neutral person.

Are all of the elements of informed consent included at 45 CFR 46.116 necessary to be conveyed, or are some elements unnecessary? . . .

All of the elements of informed consent currently required are essential to a knowing, voluntary decision in circumstances conducive to voluntariness.

To remove or weaken any of these elements is to violate guarantees given by the United States to the world community in compliance with international law on human rights. See our Section (B) Sources of law and regulatory intent, in this response.

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

No. Scientific research on a human subject without informed consent is unlawful under the International Covenant on Civil and Political Rights unless the research is for the individual's benefit in a life-threatening emergency and there is no readily available medical alternative.

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?

Yes. Written informed consent should be required for all focus groups and similar procedures. Oral consent may be appropriate for surveys found by an IRB not to involve vulnerable subjects or circumstances of vulnerability.

What principles or criteria distinguish these cases?

Focus groups are non-confidential and may endanger subjects or third parties. Surveys may involve vulnerable persons and circumstances of vulnerability, and in the case of pupils of U.S. publicly supported educational institutions implicate concurrent regulations of the U.S. Department of Education.

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

* * * * *

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent?. . .

All circumstances unless: The data cannot be traced to an identifiable person, family, or kinship group; there is no way to re-identify; no cross-linkage behavioral or social studies are involved; and strong enforcement mechanisms are in place.

Question 46: Under what circumstances should unanticipated future analysis of data that were collected for a different research purpose be permitted without consent? . . .

None. To do so would be to contravene law and commitment to the 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?

This practice should be disallowed until it can be reformed and effectively monitored. It is conducive to dishonesty and patient harm, by excess tissue collection and perhaps by excess billing. The suggested condition, "as long as the subject's identity is never disclosed to the investigator," is insufficiently protective.

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?

No circumstances unless: The data cannot be traced to an identifiable person, family, or kinship group; there is no way to re-identify; no cross-linkage behavioral or social studies are involved; and strong enforcement mechanisms are in place.

Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data?

Yes. To foster fairness, we recommend that this be accomplished under the Negotiated Rulemaking Act.

Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?

No. Public education campaigns in this context would likely be promotional and one-sided. Opt-out processes are inherently unfair and violate the requirement and substance of informed consent. Further, an opt-out process on the use of data and biospecimens would hinder transnational research by violating European Union privacy law.

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?

Informed, revocable consent in circumstances conducive to voluntariness.

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)?

This question is appropriate for the negotiated rulemaking procedure that we recommend in our response to Question 49, above.

Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

Yes. Otherwise the individual is being presented with an analog to what in contract law would be considered a contract of adhesion and therefore unconscionable.

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?

U.S. research programs, OHRP, and FDA should bar the use of biospecimens unless: Provenance is credibly shown; the specimens come from voluntary donation for specified research purposes; there was no sale or sham donation; there was informed consent in circumstances conducive to voluntariness; and the specimens should not be sold or transferred for fees or service charges that are tantamount to a sale.

Should there be different rules for that setting, and if so, what should they be?

See our answer to the first query of Question 51, immediately above.

Should they be based on the relevant requirements in the countries where the biospecimens were collected?

While local law should be obeyed, if it conflicts with or is weaker than U.S. research subject protections then use of such biospecimens should be disallowed by U.S. research programs, OHRP, and FDA.

Local law even if ostensibly protective may not be adequate, however, in light of lack of enforceability, lack of enforcement, or circumstances of human subject vulnerability.

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?

Consent rules should not be weakened or eliminated. To the extent that consent rules are strengthened, informed consent should be sought diligently and promptly.

If so, what are the operational issues with doing so?

Operational issues will arise whether or not the biospecimens and data are "grandfathered." Informed consent must be sought. Approval for use of tissues and data taken without informed consent should not be renewed unless these materials are not and cannot be made identifiable. Cross-linkage studies using such data and materials should be barred immediately even if in progress.

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? . . .

No. The concept of impracticability for a discretionary act has no meaning in the relevant law and ethics. It is no more than a way to avoid

responsibility and should be removed from the Common Rule. If it cannot be removed from the Common Rule, then guidance should make clear that in effect it never applies.

Is the number of potential human subjects the only measure of impracticability?

See our response immediately above.

V. Strengthening Data Protections To Minimize Information Risks

* * * * *

Collection of identifiable data, as well as secondary analyses of such data, poses informational risks.

As we point out above in this response, protecting the information itself is one fundamental part of the problem. The first fundamental part of the problem is how the information is obtained. Another is who can use the information for what purpose and under what circumstances and limitations. Another fundamental part of the problem is how the information is obtained—whether it is obtained surreptitiously, whether it is obtained with informed consent in circumstances conducive to voluntariness and to vindication of rights, and whether subjects are in danger of waiving their rights.

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.

We agree.

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. . . .

We agree.

Separate from the HIPAA Rules, the Privacy Act of 1974, as amended (5 U.S.C. 552a 82) binds Federal agencies to protect personally identifiable information in their possession and control. . . . In addition, there are other Federal privacy provisions that may need to be considered, but all have a limited scope. . . . 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.

We agree. Nevertheless, the Privacy Act would be violated by some of the activities contemplated in this ANPRM's data bank proposals.

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).

We agree that certificates of confidentiality may not be adequately protective. They have not been subject directly to judicial scrutiny. They pose substantial questions as to Congressional authority to override the powers of state courts to subpoena witnesses and compel production of evidence in matters of state law.

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.

We agree.

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.

We concur as to desirability of much better data security and information protection but disagree as to the adequacy of the proposed remedy.

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.

As we state in response to Question 53, the concept of impracticability for a discretionary act has no meaning in the relevant law and ethics. It is no more than a way to avoid responsibility and should be removed from the Common Rule. If it cannot be removed from the Common Rule, then guidance should make clear that in effect it never applies.

Further, it is envisioned that these data security and information protection standards would be scaled appropriately to the level of identifiability of the data.

The ANPRM correctly implies that this is a moving target. That makes the ANPRM proposals to weaken or eliminate consent and ethics review even less explicable.

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.

Agency guidance can make clear the legal and ethical problems raised by re-use without informed consent.

A. Consistently Characterizing Information With Respect to Potential for Identification

* * * * *

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?

No. HIPAA has too many consequential gaps.

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?

No.

If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?

This question should be taken up via the Negotiated Rulemaking Act.

Question 55: What mechanism should be used to regularly evaluate and to recommend updates to what is considered de-identified information? . . .

We recommend taking this up proceedings via the Negotiated Rulemaking Act.

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?

For each use: Only with full IRB review, full-IRB continuing review, and revocable informed consent by subjects, in circumstances conducive to voluntariness, with consent documents to include as complete as possible a description of ramifications of consent. Additionally, OHRP should audit all cross-linkage studies for compliance with the Common Rule. For longitudinal studies, the voluntary, informed consent of each subject should be sought at least annually and each time the study is changed in any significant way. No further information should be sought about subjects who do not sign up to continue in the study.

Should a human biospecimen be considered identifiable in and of itself?

Yes, for reasons stated in Question 56, above—because of current rapid biotechnological changes in that direction in combination with extensive growth of data mining.

What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?

Advantages: Human subjects are less likely to be left unprotected.

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)?

Yes. All types, for reasons stated above.

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. [Note omitted.] *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.*

The ANPRM posits a false dichotomy—between IRB review and data security. IRB review is intended in part not to secure the data but to ensure that proper protections are in place.

As we state elsewhere, informational risks apply to collection and use as well as to security. The ANPRM would remove a great deal of collection and use from IRB scrutiny.

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. [Note omitted.] . . .

As we point out elsewhere, HIPAA security requirements are not enforced adequately and provide no individual remedy.

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.

We disagree. The use of "trusted third parties" does not eliminate the hazard of security breach or create an enforcement tool and individual remedy where none exists.

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

We agree on the need for stronger enforcement.

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?

All applicable data security and information protection standards should apply to all data and biospecimens unless these standards weaken existing protections.

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?

Investigators who have fulfilled their promises of confidentiality and data protection should have no difficulty.

How should the new standards be enforced?

By appropriate U.S. Government agencies.

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?

No. As we explain elsewhere in this response, HIPAA is not protective. It provides no individual remedy. It is no substitute for IRB review to ensure that that collection and use are ethical and lawful.

Are such standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research?. . .

Data security and information protection need to be strengthened for all human subjects research.

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)?

Yes, because the interaction might take place in circumstances where confidentiality and/or voluntariness cannot be assured. Data-security and information-protections of the type proposed in the ANPRM do not deal with information collection or with who can authorize information access for what purpose. These possible problems necessitate full IRB review in addition to special, perhaps standardized, measures where research subjects are vulnerable.

Question 61: Are there additional data security and information protection standards that should be considered?

Yes, as we state in response to Question 60, above.

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.'')?

Federal data collection and use vary greatly in method and purpose and, as with HIPAA, allow substantial exceptions to privacy and confidentiality. Mandatory standards for data security might be feasible, but mandatory common standards for access and use would require statutory as well as regulatory change. An attempt to establish a government-wide standard might well result in a weakening of current standards.

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?

This is a strong possibility, inasmuch as local rulings on HIPAA issues are made by persons who without legal training try to parse the HIPAA regulations without reference to the ethics of research or to law.

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?

Yes, and it should be directly enforced by an appropriate, neutral government agency.

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-identifying such data a sufficient protection, . . .

No. There is no meaningful monitoring and enforcement mechanism.

. . . 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?

Yes. In all instances. Note, however, that HIPAA leaves wide gaps, including for government administrative inquiries, fund-raising, and law enforcement.

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?

Yes.

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?

Auditing in this context should be a U.S. Government function, to be carried out by federal officers and not by contractors or grantees..

Should an institution have flexibility to determine which entity or entities will have this oversight responsibility for their institution?

No. This requires regulatory specificity, to ensure that safeguards are not under the control of entities and individuals whose institutional interests conflict.

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 *non-research purposes*?.	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 *research purposes*?.	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.

We believe that biospecimens banks can be developed and operated in ways that are respectful of the rights of human subjects. SEE, e.g., Elisa Eiseman & Susanne B. Haga, HANDBOOK OF HUMAN TISSUE SOURCES: A NATIONAL RESOURCE OF HUMAN TISSUE SAMPLES (1999).

Table 1 describes no such arrangement. Table 1 describes a system for lifetime surrender of privacy rights with no remedial recourse. The table leaves open the questions of who would authorize whom to use which data under what circumstances. Especially because of interest in behavioral genetics and because of law enforcement interest in biomedical science, the concerns implicated by Table 1 cannot be limited to those involving biospecimens alone. The system described here lends itself to the tracking of individuals. The system described is

unprotective of human subjects. No IRB would review or monitor the circumstances or substance of consents to future research, which could be highly invasive of privacy, or limit who might use these data for what purposes. For those situations where individuals are asked to consent there are no standards to ensure that consent is knowing and voluntary in circumstances conducive to voluntariness, that subjects are informed that they have no substantive rights concerning use of their information, and that they cannot withdraw consent.

Law enforcement and security agencies are accumulating extensive collections of biospecimens and personal information—all without their subjects informed consent and often without a warrant. The system described in Table 1 would leave these subjects unprotected and might open their records to additional uses without their knowledge and consent.

Substituting the Table 1 system for oversight and case-by-case analysis would leave human subjects protection programs with more regulatory quandaries than they face now. Moreover, it would raise new and difficult questions under the Privacy Act.

VI. Data Collection To Enhance System Oversight

* * * * *

We are considering a number of changes . . .

(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.

An effective, compulsory adverse-effects reporting system to bolster FDA and OHRP capabilities has long been needed. It is important to remember that the needs of data and safety monitoring entities are individualized to the study. Designers of a Web-based system should be attentive to Privacy Act concerns and to human factors concerns that might render it useless.

It is important to remember also that data and safety monitoring entities do not always act promptly or at adequate intervals and do not always report the reasons for their recommendations. These are problems that can be countered by agency guidance.

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.

Given the extent of personal information used by data and safety monitoring entities, this goes far beyond the scope of this rule-making and raises Privacy Act issues and grave questions of civil liberties This proposal would establish a data bank that could be exploited by researchers without research subjects' express consent but would add nothing to the enforcement of the Common Rule or the rule's FDA implementation. This proposal runs counter to the statutory obligation to protect the rights of human subjects of behavioral and biomedical research.

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?

No. Agencies can deal with this problem through guidance.

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 . . . ? . . .

Not in the aggregate. That is useless information. But see our response to Question 68(b), immediately below.

b. What additional data, not currently being collected, about participants in human subjects research should be systematically collected . . .

The numbers of subjects recruited and the number of individuals declining to be subjects should be reported to cognizant funding agencies or to the FDA, as appropriate, for each study involving human subjects. These numbers should be made public in a timely way that shows for each study the project itself, the site, the research population, the sponsor, the cognizant IRB, and the numbers. Academic administrators, IRB's, program officers, and agency enforcement officers can use these data as clues to whether coercion, undue influence, failure of understanding, or other factors suggest adequate or inadequate regard for protection of human subjects in specific situations. These data should be collected regularly in a way that can be used for regulatory enforcement.

. . . in order to provide an empirically-based assessment of the risks of particular areas of research or of human subjects research more globally?

An "empirically-based" assessment does not contribute to the specific requirements of enforcement, which as a matter of due process must be case-by-case, based on specific circumstances.

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)?

The reporting requirement that we recommend in response to Question 68(b) should apply to all 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?

Requiring IRB's to make reasoned decisions on the record, the Administrative Procedure Act standard, would provide an information base checkable by OHRP, FDA, and other cognizant agencies.

OHRP should verify the validity and accuracy of assurances.

Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subjects protections.

An "empiric approach," implying surveys and categorization of risk statistically by research method and then prioritizing enforcement attention by research categories, is no substitute for case-by-case enforcement. We believe that all of science has its conscientious practitioners and its offenders, although it is true that some kinds of research and research settings should self-evidently warrant more scrutiny.

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 agencies?

Standardization and improvement of adverse events reporting are useful, but for immediate protection of research subjects and not for an "empiric" approach to regulation.

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?

With regard to FDA-related trials, the answer is: Not yet, but we are hopeful. In these regards the FDA needs resources and a show of regulatory teeth. The service should be expanded to include other biomedical trials, including those that are not FDA-regulated.

VII. Extension of Federal Regulations

* * * * *

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?

We assume that there is a mistake in this question, inasmuch as considerable academic research is privately funded and FDA-regulated connection. Academic and commercial research on human subjects is regulated some states—as in Maryland, for example, which follows the Common Rule.

We believe that trying to close the gap would be less protective. The question would open substantial political dispute over Congressional powers; as we suggest in response to Question 74, below, the effect of opening the question would destabilize the human subjects protection regulatory regime for a long time to come. At the same time, we believe that where the gap exists in the United States human subjects will be better protected by institutional attention to tort liability exposure than by opening prolonged questions over Federal power.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

* * * * *

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

Agencies, their grantees and contractors, and some scholars concerned with research subject protections often are ignorant, dismissive, or contemptuous of relevant law that binds the entire government and that may be protective of human subjects.

The worst example in recent years is the notorious, subsequently withdrawn "torture memo," which was assumed to authorize numerous violations of human rights law and humanitarian law. Among those violations was experimentation by U.S. personnel and by contractors on captives to develop and

enhance techniques of hostile interrogation. SEE Steven H. Miles, OATH BETRAYED: AMERICA'S TORTURE DOCTORS (2d ed. 2009) xiii, xvi, and Bradley Olson & Steven H. Miles, *The American Psychological Association and War on Terror Interrogations,* Appendix 2, *in* id. at 187-198.

We have heard of attempts by National Children's Study investigators to bully public school districts into disclosing pupils' behavioral records in violation of statute and U.S. Department of Education regulations.

FDA's enforcement of human subjects protection is much stronger than that of OHRP. This is attributable partly to differences in resources and willingness to enforce.

These observations notwithstanding, we believe that it is not so much differences among the agencies as it is differences among the research communities and their research traditions that result in stronger or weaker protections for research 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?

Agencies differ considerably. FDA and the International Conferences on Harmonization rules, to the extent that the ICH rules have been given legal effect, exert considerable leverage on research related to the marketing of drugs, biologics, and devices in the much of the developed world. As implemented by member states of the European Union, ICH human subjects protections are supposed to apply wherever their nationals (individuals, corporations, and agencies) are engaged—at home and abroad. Moreover, the EU regime requires independent, specially trained inspection cadres. The difficulty is that ICH in these respects applies only to clinical trials. Control of other research, as in a good deal of research under the Common Rule, is loose.

Countries differ greatly. There are a few highly important universal requirements, mostly notably the International Covenant on Civil on Political Rights no-exceptions requirement of informed consent as a precondition for research on human subjects. Almost all the world's countries—whether developed or otherwise—have ratified the Covenant; they have told the world they will comply and have subjected themselves to a reporting-and-investigations regime. Similarly, the Geneva Conventions and their Additional Protocols are obligations of governments worldwide. But governments inevitably are compartmentalized; few government officials, researchers, research administrators, and research agencies are aware of their government's commitments and obligations. Fostering local community pressures to minimize the role of individual informed consent would violate international human rights commitments by the host country as well as by the United States.

Some researchers and even some bioethicists dismiss such law as irrelevant or repeat the myth that there's no law out there.

Because of their vulnerability, research on refugees poses special ethical challenges to researchers both in and outside the United States.

The United Nations High Commissioner for Refugees (U.N.H.C.R.) is charged with protecting the safety and confidentiality of refugees. With increased transportation access to refugee camps and increased biomedical and behavioral research interest in refugees and in pertinent public health issues, the U.N.H.C.R. has been reminding researchers of their obligations—especially relating to confidentiality, voluntariness, and informed consent. SEE e.g. : Tricia Hynes, The issue of "trust"'or "mistrust" in research with refugees: choices, caveats and considerations for researchers, Working Paper No. 98, PDES Working Papers, 30 November 2003 U.N.H.C.R. <http://www.U.N.H.C.R..org/3fcb5cee1.html> (last visited Aug. 31, 2011); U.N.H.C.R. HANDBOOK FOR THE PROTECTION OF INTERNALLY DISPLACED PERSONS (IDPS), June 2010 <http://www.U.N.H.C.R..org/cgi-bin/texis/vtx/search?page=search&docid=4c2355229&query=handbook%20for%20the%20protection> (last visited Aug. 31, 2011); U.N.H.C.R., OPERATIONAL PROTECTION IN CAMPS AND SETTLEMENTS: A REFERENCE GUIDE OF GOOD PRACTICES IN THE PROTECTION OF REFUGEES AND OTHER PERSONS OF CONCERN, Legal publications, 1 June 2006 <http://www.U.N.H.C.R..org/cgi-bin/texis/vtx/search?page=search&docid=448d6c122&query=operational%20protection%20camps%20settlements (last visited Aug. 31, 2011).

Interest in refugees as a research population includes behavioral science, social science, and clinical trials. Not all the research is specific to problems distinctive to the individual subjects; some of this research is within the United States; some of it is overseas. A clinicaltrials.gov check with the search term "refugee" turned up 17 projects. http://clinicaltrialsfeeds.org/clinical-trials/results/term=refugee (last visited Aug. 31, 2011).

We press our point concerning informed consent because(1) it is at the heart of respect for the dignity of the individual, and (2) even in bioethics we hear recurrent rationalizations that because human subjects research is for community benefit it may be conducted where individual informed consent has no cultural meaning. It seems odd that researchers would decide to skip or get around informed-consent requirements abroad in countries (almost all the world's countries) that are committed by treaty or even additionally by their constitutions (South Africa and Malawi, for examples) to informed consent as a precondition for research on human subjects. Of course, law is sometimes ignored. As an ethical matter:

> A researcher should not pick and choose which elements of a culture he or she accepts based upon the way in which it will help or hinder the research. "Cross-cultural sensitivity" does not give an experimenter license to bend and break norms of professional conduct . . . . Experimental protocols may need to pass two ethical tests, a general ethical test of respect for persons and a more specific test of how true respect may be obtained in a particular culture.
>
> This specific ethical test would not abandon basic values but rather ask how such values are to be enfleshed in culturally different contexts. . . . On occasion, . . . a true impasse might arise because of a genuine clash of values themselves. At such times, the experimenter may very well find it ethically necessary to abandon a particular experiment in a particular culture. Such cross-cultural sensitivity may benefit not only the subjects of the experimentation but the ethical person who is the experimenter as well.

Thomas A. Nairn, *The Use of Zairian Children in HIV Vaccine Experimentation: A Cross-Cultural Study in Medical Ethics*, *in* ON MORAL MEDICINE 919, 928-929 (Stephen E. Lammers & Allen Verhey eds., 1998).

As we note above, the right to informed decision as to whether to be a research subject is established in human rights law, and the World Health Organization's Revised International Health Regulations do not accept a public health rationale for violation of human rights.

Local legal and political differences are very important. Corruption remains a serious problem. Vindication of legal rights is hazardous or impossible in many countries where research is conducted. Unfortunately, from our point of view, these problems do not seem to have impeded research activities where human subjects protections are weak or non-existent.

What are the most important such differences influencing the conduct of research?

The President's Commission on Bioethical Issues recently heard testimony that some universities, companies, and researchers seek to go where research is less regulated. For U.S. researchers and research entities, the problem is exacerbated because the U.S. Government lacks sufficient will, resources, or both to validate assurances whether at home or abroad, and to adequately audit domestic and foreign clinical trials.

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally?

No. The nature of research varies widely among the agencies. Seeking to do this would destabilize rather than enhance the existing regulatory system and

would do so for a very long time. However, each Common Rule agency—in a public process—should pay close attention to and comment as warranted on guidance proposed by other agencies, and each should inform its research constituencies of the existence of possibly relevant guidance from the other agencies.

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)?

No, for the reasons stated above in our response to Question 74, above, and for the reasons stated in the Michigan State University faculty response (attached) to a solicitation of comments on equivalent protections for U.S. international research. That proposal lent itself to the likelihood that no more than paperwork compliance would be deemed acceptable. The comments were that conditions vary so widely that in many instances only case-by-case evaluation can suffice.

IX. Agency Request for Information

* * * * *

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

The ANPRM's length, discursiveness, vagueness, topical breadth, repetition, convolution, and intermingling of assertions and questions, many of them multi-part and overlapping, make response-to-the-number impossible. This submission responds to significant, unnumbered questions scattered through the ANPRM's topical discussions as well as to numbered questions. For clarity, we show in italics the ANPRM texts, including question number if there is one, to which our comments respond. The Administrative Procedure Act requires that all responses receive full consideration.

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 . . . .

See our Section (E), General concerns, immediately below, and our Section (F), Summary and conclusions, thereafter.

(E) General concerns in response to the ANPRM.

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.

Among others, these problems warrant OHRP's attention in furtherance of the mandate to protect prospective and current human subjects of research; this listing is in no particular order.

Openness, transparency, public accountability: Agency guidance should provide for timely public disclosure, in a way that is readily accessible by the public, of: Full texts of assurances; names, highest degrees, relevant affiliations, fields of work, and IRB-service dates of IRB members and alternates; names and contact information for external IRB's relied upon by the institution; IRB meeting minutes, redacted only for trade secrets and for advice of the IRB's own legal counsel to the IRB, but with votes, statements, and discussions recorded by member name.

Convened meetings: The Common Rule calls for a deliberative IRB process, in convened meetings, implementing the statutory mandate. Too often, IRB business is conducted by teleconference or largely by other forms of electronic meetings rather than by face-to-face meetings. By ordinary dictionary definition, convened meetings and deliberation are face-too-face assemblies, in which participants can assess each other's degree of involvement and concentration. Agency guidance should require that IRB convened meetings are face-to-face, in-person meetings.

IRB member access to IRB records. All IRB members should have access to all IRB records concerning proposed and current protocols, whether or not subject to expedited review or to review by primary reviewer and whether or not before the IRB for renewal only.

Grounds for decision: Agency guidance should make clear that each IRB decision should be a reasoned decision on the record. This is the Administrative Procedure Act standard and is a safeguard against arbitrary and capricious acts and omissions whether favorable or unfavorable to research proposals.

Conflicts of interest, including conflicts of affiliation and loyalties: Institutional officials, IRB administrators, and staff: Agency guidance should make clear: When the institutional official is the same person who is in charge of the institution's research program there is a rebuttable presumption of a disabling conflict of interest in conflict with the institution's assurance; for administrative purposes and in connection with the substantive work of the IRB, IRB administrators should be free

of conflicts of interest and should be responsible only to the IRB and to the institutional official; IRB staff should be free of conflicts of interest and should be responsible only to the IRB administrator.

Conflicts of interest, including conflicts of affiliation and loyalties: IRB chairs and members, including alternate members: Agency guidance should make clear: IRB chairs, administrators, and staff should be free of conflicts of interest; IRB members must represent the interests of prospective and current research subjects in connection with the proposed or ongoing research and are not on the IRB as representatives of their particular academic, scientific, medical, or other professional disciplines; this admonition applies as well to individuals who are alternate members of IRB's.

Conflicts of interest, including conflicts of affiliation and loyalties: Research subject advocates and recruiting of subjects for research: Agency guidance should make clear that a research subject advocate's primary loyalty in human subjects research should be to prospective and actual research subjects. Agency guidance should make clear that persons recognized by IRB's, investigators, or sponsors as advocates for research subjects should not be involved directly or indirectly in the promotion and publicity of any human subject research and/or recruitment of research subjects. Agency guidance should make clear that the employment of a research subject advocate for pay or as a volunteer by any entity that sponsors, conducts, or advocates any human subjects research should be disclosed to IRB's, investigators, and prospective and actual research subjects. Aguidance should make the involvement of a research subject advocate who directly or indirectly and whether working directly or indirectly for pay or as volunteers for any entity that sponsors or conducts research on human subjects

Conflicts of interest, including client conflicts and other conflicts of affiliation and loyalties: Lawyer participation in IRB's: Lawyers are under continuing professional discipline to advocate for the interests of their own and their law firms' current and former clients; therefore Agency guidance should make clear: Lawyers who participate in IRB's should disclose their relevant client interests and should recuse in the event of conflicts; institutional counsel should make clear that their professional obligation is to their institutional client and not to the IRB or research subjects; lawyers who are free of client, institutional, and other conflicts may serve usefully as IRB members but should make clear that they are not attorneys to the IRB.

Intimidation and retaliatory conduct: Agency guidance should make clear that intimidation and retaliation for good-faith IRB decisions and attempts to thwart good-faith IRB decision-making violate the institutional obligation to maintain a human subjects protection program.

Agency procedures should provide for the receipt of and response to complaints of such action.

Informed consent as a precondition for research on human subjects: The rule should be amended to eliminate all provision for or implication that informed consent is waivable except by the individual research subject.

Exculpatory clauses: Agency guidance should make clear that any consent-form language that could have the effect of dissuading research subjects from the exercise of their rights is prohibited.

Research injury legal terminology: The rule should be amended to correct an obvious error based on drafters' misunderstanding; replace the term "negligence," which is only one form of tort, with "wrong," which is broadly inclusive. The rule should be amended to eliminate the reference to "compensation" in connection with research injury; the term is confusing and unnecessary in this provision and is often mistaken by IRB's to refer to something in return for being a research subject.

Legally authorized representatives of research subjects and individuals being recruited as research subjects: Agency guidance should make clear to institutions, IRB's, and investigators the importance and necessity of a good-faith effort to ascertain that any person who would be recognized as a legally authorized representative under the Common Rule is in fact a legally authorized representative. The FDA already has given this requirement regulatory effect.

F. Summary and conclusions.

The ANPRM rationale relies mainly on highly questionable assumptions and a biased, largely one-sided selection of relevant literature and reflects inadequate consideration of how the proposed changes would play out in practice.

The ANPRM reflects disregard of vulnerability, contra statutory intent and the Belmont Report. Contrary to statutory mandate and the Belmont Report, the ANPRM proposes to eliminate or cut back the 45 C.F.R.subpart A requirement for special protective attention to all especially vulnerable prospective and actual research populations. The ANPRM proposal would leave in place the very important protections in subparts B, C, D, and E, but those cover far from all prospective and actual subjects who are especially vulnerable.

Some of the changes proposed as enhancing protections are based on misunderstandings or ignorance of the relevant fields or study and relevant law. Most of the changes recommended would weaken rather than implement or enhance statutorily required protections for human subjects of behavioral and biomedical research. Moreover, most of the proposed changes would unnecessarily hinder rather than stimulate or facilitate behavioral and biomedical research.

We believe that, as the ANPRM drafters suggest, facilitating data security is desirable and that, with proper protections as we suggest above, central IRB's can be desirable to bring needed expertise into assessment of risk in certain areas of biomedical research. Progress in these areas can be made through agency guidance. But these topics deserve for considered attention than the drafters gave them in this ANPRM.

Amending the Common Rule as recommended in the ANPRM would for the most part:

- Substantively weaken vital protections and endanger prospective and actual human subjects, especially those who are vulnerable to coercion or undue influence, those who would be endangered by unwanted disclosures, and those who are not in a position to make informed, voluntary decisions or to vindicate their rights;

- Open opportunities for widespread, massive invasions of privacy, ostensibly for research;

- Substitute for relatively simple, relatively easily interpreted, and generally workable regulations and compliance norms a convoluted, confusing, and unnecessarily specific regulatory structure that requires sponsors, investigators, and IRB's to engage in time-consuming, fine-point rule-parsing and that invites attempts to evade the statutory intent to protect human subjects of research;

- Exacerbate the problem of reliance by U.S. researchers, institutions, and transnational research collaborators on satisfying paperwork requirements rather than on good-faith decision-making to protect human subjects;

- Put research institutions and investigators in legal and professional peril and greatly enlarge their liability exposure should they wrongly assume, as typically many do, that Federal research regulations constitute the whole of relevant law and that informed consent could be minimized or eliminated in many circumstances; and

- Invite widespread distrust of behavioral and biomedical research on human subjects and deter subject recruitment as it becomes known that ethics review of individual studies is or might be minimized or eliminated.

The ANPRM proposals on balance:

- Would not enhance but rather, contrary to law, eliminate protection for many research subjects and weaken protection for many others;

- Would not reduce but rather would increase burden, delay, and ambiguity by putting institutions and investigators at their legal and professional peril by substituting personal discretion and rule-parsing for actual institutional and regulatory oversight, and would consequently increase liability exposure; and

- By coupling reduction of oversight and fostering of data-gathering without individual, adequately informed consent would prompt widened distrust of conscionable science as well as of those research activities that deserve distrust.

We will be pleased to be of assistance.

Sincerely,

For Citizens for Responsible Care and Research:

Gerald S. Schatz, J.D.
(Of the Bars of the District of Columbia and Pennsylvania)
Vice President, CIRCARE

Reply to: Elizabeth Woeckner, M.A.
President, CIRCARE
1024 N. 5th S.
Philadelphia, PA 19123-1404
E-mail: lizwoeckner@mac.com
Telephone: 267.671.8212

Or: Gerald S. Schatz, J.D.
Vice President, CIRCARE
10788 Brewer House Rd.
Rockville, MD 20852
E-mail: geraldschatz@att.net
Telephone: 301.984.6142

Appendix: Submissions to the Presidential Commission for the Study of Bioethical Issues.

A. Public comment (uncorrected transcript)

February 28, 2011:

MR. SCHATZ:

Good afternoon. My name is Gerald Schatz. I'm a Vice President of CRCR, the Citizens for Responsible Care and Research, a non-profit organization, and I taught university law and ethics of human subjects research.

I think the Commission will find it very helpful, as it goes about this task, to take a look at the current state of aggregation of medical record systems, and the state and capabilities of the data mining industry, which is something we have with us now.

March 1, 2011:

MR. SCHATZ:

Thank you. My name is Gerald Schatz and I am a lawyer and retired professor, Assistant Professor of Ethics and Law at Michigan State University. I want to address two things very quickly.

One is the theme of vulnerability and its recognition. We have gone from an era of very reflective and I think very decent recognition of the moral obligations of researchers to an era of discussion of regulatory burden. I think that is unseemly.

The second point is that there is law out there. The bioethics community has been oblivious to it but there is international law. There is the International Covenant on Civil and Political Rights the United States ratified in 1992 and it makes informed consent an absolute requirement, no exceptions, not even in emergencies, subject to those normal legal fictions of consenting for the incapacitated patient to medical care and so forth.

Additionally, the Geneva Conventions and additional protocols to the Geneva Conventions make research very, very difficult or prohibited altogether for those individuals who are caught up in the war and armed conflicts.

Michigan State University faculty responded to the OHRP request for comment in 2005 on equivalent protections. I will be pleased to provide that comment and those citations and some additional materials to the Commission. Thank you.

B. Citizens for Responsible Care & Research, Inc, Public comment [written] in response to the Commission's March 2, 2011 Federal Register notice. <Attached file: public_comment_20110502.pdf>

C. Referenced documents submitted by CIRCARE to the Commission:

1. Tom Tomlinson, et al., response to Office for Human Research Protections solicitation of public comment on Proposed Criteria for Determinations of Equivalent Protection; 2005. <Attached file: ohrpecmt2005may.pdf>

2. Gerald S. Schatz, *Diritto internazionale e bioetica [International law and biomedical ethics, in* ENCICLOPEDIA DI BIOETICA E SESSUOLOGIA (Giovanni Russo, ed., trans.; Elledici – CIC Edizioni Internazionali Leumann – Roma 2004) at 660. <Attached file: dict1schatz.pdf>

3. Gerald S. Schatz, *Are the Rationale and Regulatory System for Protecting Human Subjects of Biomedical and Behavioral Research Obsolete and Unworkable, or Ethically Important but Inconvenient and Inadequately Enforced?,* 20 JOURNAL OF CONTEMPORARY HEALTH LAW AND POLICY 1-31 (2003). <Attached file: schatz2003jchlp.pdf>