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Jerry Menikoff, M.D., J.D.
Director
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Department of Health and Human Services
1101 Wooten Parkway, Suite 200
Rockville, Maryland 20852

Re: **Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, Federal Register Vol. 76, No. 143, July 26, 2011**

Dear Dr. Menikoff:

As an institution involved in a broad range of research activities and one that is committed to the protection of human subjects, Harvard University welcomes the opportunity to provide comments on the advance notice of proposed rulemaking ("ANPRM" or the "Notice") entitled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators[1]." As discussed in the background statements of the ANPRM, research has evolved and diversified since the Common Rule ("CR") was adopted, and Harvard agrees that it is important to reevaluate and, as necessary, update the regulatory framework.

[1] Federal Register 76, 143:44512, (PROPOSED July 26, 2011).

Harvard applauds the ANPRM's goal of reducing or eliminating unnecessary oversight responsibilities and of helping to streamline IRB processes in order to free up IRB time and energy for vigorous review and monitoring of research that may pose risks to subjects. An example of this is the ANPRM's recognition that certain minimal risk studies need not be subject to strict federal oversight and in-depth review. Social and behavioral research often involves a lesser degree of risk than biomedical research and it is important to gauge the level of risk prior to making determinations as to the appropriate level of oversight. And yet, we cannot lose sight of the overarching need to protect research subjects. Harvard's comments seek to highlight areas in which the balance between expediency and risk to subjects may be threatened by the ANPRM proposals and where caution and further study may be warranted.

The ANPRM also proposes major changes to the ways in which future research may be allowed using identified and de-identified personal data and biospecimens. As described more fully below, Harvard generally agrees that there is a need for greater public education about the nature and scientific value of future research uses, and recommends tightening protections to prevent unconsented re-identification of data and biospecimens. At the same time, however, Harvard is opposed to the idea that all or nearly all such future research uses must be conditioned upon subjects' "general consent for future research uses."

Due to the extensive nature of the proposed changes to the Common Rule, the comments below are organized in sections mirroring the sections of the ANPRM, with an emphasis on proposals and/or questions of particular concern to our human subjects research investigators, IRB members and administrators, and, we believe, to the human subjects who participate in our research. Where the comments directly relate to enumerated questions in the ANPRM, the questions are cited for ease of reference.

II. Ensuring Risk-Based Protections

With respect to high-risk studies, Harvard agrees with the premise set forth in the ANPRM – namely, that research involving greater than minimal risk should continue to be reviewed by a full convened IRB. However, with many of the suggested changes in the proposed rule dependent on the determination of risk level, a more precise definition of minimal risk is needed. The definition of minimal risk must be nuanced: a definition that equates minimal risk with procedures alone would be an oversimplification. Such a definition may well lessen human research protections.

In determining minimal risk, the IRB's evaluation of the potential harms and discomforts of research should take into account the nature of the study procedures and other study characteristics, as well as the steps taken to minimize risk. In its estimate of research-related risk, the IRB should also carefully consider the characteristics of subjects to be enrolled in the research, including an evaluation of subject susceptibility, vulnerability, resilience, and experience in relation to the procedures, and the anticipated harms and discomforts of research involvement within the context of their environment. This is of particular significance in the arena of international research, where perception of study risks may vary according to the research setting.

A. Revising the Approach to Expedited Review

Harvard agrees that the Expedited Review list should be reviewed and updated on a regular basis, and that the default presumption should be that a study that includes only activities on the list is a minimal risk study and thus eligible for expedited review.

Question 1: Harvard suggests the following proposed definition of minimal risk, which recognizes that risks are procedure-specific and population-dependent, but includes a fixed notion of "acceptably-low" risk. If the expected harms and discomforts of the proposed research on the particular study participants were judged to fall below this acceptably low risk threshold, then the research would constitute "minimal risk:"

> ***Minimal Risk means that the probability and magnitude of harms or discomforts introduced solely by the research are not greater in and of themselves than those familiar and routine experiences ordinarily encountered in the daily life of the general population where the research is being conducted or during the performance of routine medical, dental, psychological, or educational examinations or tests.***

Guidance should address what risk mitigation mechanisms may be considered by IRBs when determining that proposed research is minimal risk.

Question 2: The ANPRM fairly questions the need for continuing review of research approved by expedited review. In studies in which there is ongoing interaction with subjects, however, continuing review serves as a "fail-safe" mechanism to capture protocol changes or minor problems that an investigator inadvertently may fail to bring to the attention of the IRB or that only become apparent once a study has begun. For this reason, Harvard suggests that there should be a two-year default for continuing reviews of research eligible for expedited review, but the proposal should allow for more frequent review within the IRB's discretion. For example, as student-conducted research generally has a shorter event horizon than other types of research, an institution may wish to review such research more frequently than once every two years.

Question 3: The ANPRM's recognition that elements of complex projects warrant separate consideration seems appropriate. The proposal to eliminate required continuing review of studies in which the remaining activities are limited to data analysis (even if

identifiers are retained), however, raises concerns that such a default position may be less effective in assuring protection for research subjects. For continuing review of research that requires initial review by a convened IRB, Harvard recommends that there should be continuing reviews as long as the research involves identifiable data. Also, as described in the response to *Question 2*, above, a two-year cycle of review is preferable to elimination of continuing review.

***Question 4*:** Changing the regulations so that only "reasonably foreseeable risks or discomforts" are considered would be a useful clarification that would help IRBs avoid focusing on theoretically possible, but highly improbable, scenarios when considering whether a risk requires mitigation.

***Question 5*:** Developing criteria to "determine with specificity" what psychological or other non-physical risks are greater than minimal is unnecessary and could be counterproductive because the fact patterns presented by research proposals are infinite and varied, and a core function of the IRB is to make this determination on a case by case basis. Over time, IRBs develop familiarity with the research programs at their institutions and the settings in which that research is conducted, and their knowledge base facilitates accurate characterization of new studies.

***Question 6*:** In rare circumstances, a survey study may be classified as greater than minimal risk; the characteristics of the study population should be a factor to be taken into account. A study of competent adults who may have experienced a psychological or physical trauma could benefit from full IRB consideration even if the study methodology is only a survey. For the reasons stated in answer to *Question* 5, this is an example of the type of judgment an IRB makes (and should continue to make) on a case by case basis.

Question 7: Categories of study that should be added to the list include: behavioral economics studies that involve game playing, either in small groups or on computers, in which participants engage in activities that result in their losing or gaining small sums of money, whether real (provided by investigators) or imaginary. Implicit attitude studies, attention gaze studies, computer game studies and other common interventions that permit investigators to gauge responses to harmless stimuli should be added as well. However, studies that include feedback to subjects about their own performance on measures that could be perceived as having clinical validity or implications (such as studies of cognitive function) may warrant additional scrutiny by the IRB and may not always be judged to present minimal risk.

Question 10: The ANPRM questions whether it is necessary to consider all the criteria for IRB approval of research at 45 CFR 46.111 when research qualifies for expedited review. Harvard recommends that the approval criteria for studies that qualify for expedited review should be the same as the criteria for studies approved by a convened IRB. It should, however, be made clear that IRBs have discretion to apply or not apply criteria, as appropriate. The current regulations already provide sufficient flexibility through the inclusion of "when appropriate" at 46.111(a)(1)(ii), (a)(6) and (a)(7). Consideration may be given to adding "when appropriate" to the introduction at 46.111(a) and/or to providing revised guidance indicating how IRBs should apply 46.111 when reviewing research under expedited review procedures.

Question 11: While Harvard appreciates the intent of the suggestion that expedited review might not be required to be performed by a member of the IRB committee, current practice seems satisfactory and not burdensome: at many universities, the IRB is comprised of faculty members, academic administrators with relevant experience and work responsibilities, and IRB staff members with sufficient experience to carry out expedited reviews.

The presence of the staff members on the IRB is beneficial because it serves as a means for the in-depth considerations that take place at convened meetings to inform the expedited reviews that are carried out primarily by the IRB staff committee members, and also as a means for the full Committee to be informed about the large volume of expedited review cases (which can, in our experience, constitute more than 90 percent of cases at most university IRBs that are not handling biomedical studies).

Question 13: Harvard does not favor mandatory reporting by IRBs when they choose to override provisions for expedited review. Adding such a requirement may negatively impact the IRB-investigator relationship, but with no measurable benefit to offset such an impact. One of the strengths of the current expedited review process is that it allows IRBs to determine the appropriate level of IRB review for non-exempt human subjects research. IRBs should continue to have the discretion to determine the appropriate level of review.

A requirement to report IRB activities that exceed the regulatory minimum also directly contravenes one of the goals of the ANPRM: to reduce burden and delay. Such a requirement would unnecessarily burden institutions and regulatory authorities. Not only would reports need to be prepared and submitted, but presumably they would need to be reviewed and assessed as well, thereby creating additional paperwork and transaction costs, as well as straining already limited human and institutional resources.

In addition, unnecessary administrative burden could be reduced by eliminating the requirement that IRBs review complete applications (i.e., grant applications) for support[2] for all research submitted to the IRB. The notion that review of complete grant application will enhance human subjects protections is flawed, in our experience. Review of grant applications appears not to be undertaken consistently across all institutions.

[2] Protection of Human Subjects, 45 C.F.R. part 46.103(f) (2009).

The grant applications themselves offer a static view of proposed research at a point in time that is often long before actual implementation; the applications are not amended once the human subjects research funded under them is refined and revised. Institutions should continue to be required to assure that researchers correctly implement funded research, but we would recommend that current requirements for congruence review of grant applications prior to submission be abandoned as ineffective and inefficient. This is a proposal not contained in the ANPRM, but we suggest it should be included in the final revised regulations.

B. "Excused"/Exempt Research

Questions 14-17: Although Harvard concurs that the "exempt" category of research under the Common Rule needs to be re-examined and perhaps expanded, we are concerned that the proposals for expansion are overly broad. In certain instances, the ANPRM inappropriately focuses exclusively on the method of the research, rather than the subject matter of the research. A preferable approach, and one that is more protective of human subjects, would take into account the nature of the research and subject population, as well as the research context. In this way, behavioral surveys of drug use, sexual and other abuse, HIV infection, STIs and illegal activities and studies involving deception would be excluded from the excused list. Additionally, the list should account for the fact that not all competent adults are similarly situated with respect to all research studies. For example, a competent adult suffering from the psychological effects of a traumatic experience enters into a study about mood and outlook from a very different position than a competent adult who is not suffering from similar psychological effects. A carefully selected and diverse group of experts should participate in any efforts to revise the "excused" (and under existing regulation, "exempt") categories of research.

If, indeed, survey research involving competent adults is retained as "excused", there must be some effort to define what is meant by a "competent adult." What constitutes competency varies from state to state, suggesting that this proposal would introduce greater variability in the application of the Common Rule across institutions, thus increasing complexity and transaction costs.

Administrative Review and Shifting Responsibilities

Question 19: For research submitted under the "excused" category, we believe that there should be at least a one week waiting period from submission before a researcher may commence research. The ANPRM's proposal to eliminate administrative review represents a major shift in responsibility from the IRB, which in most cases currently conducts such reviews, to researchers, who currently rely on IRB administrative review/consultation. Because this is a new responsibility for researchers, a waiting period would help to ensure that researchers are applying the rule correctly and would avoid the scenario in which research that requires a higher level of review commences before there is an opportunity for the IRB to identify and review it.

Retrospective Audits of Excused Research

Question 21: It is unclear from the ANPRM how the one-page registration form that would replace the IRB administrative review process for "excused" research would provide information adequate for an institution to perform retrospective audits of excused research. The time lag between registration by the researcher and eventual audit by the IRB would necessitate reconstruction of the facts and circumstances by the IRB after the fact, and may prove more burdensome on the IRB than the status quo, which involves informal consultation and

administrative review at the beginning of the process. Further, the ANPRM proposals do not clarify what the expectations should be when IRBs discover activities that were inappropriately registered as "excused." Post hoc monitoring may be recommended as part of an institution's research quality assurance program, but should not be implemented as a compliance activity that results in sanctions or penalties for investigators who acted in good faith, nor should it result in reporting by their institutions to OHRP. Institutions should be encouraged through guidance, rather than regulatory mandate, to establish and engage in ongoing quality assurance and improvement activities. Allowing for flexibility in the design and conduct of an institution's quality assurance mechanisms would better account for local variability and would foster greater success in monitoring and addressing noncompliance issues.

III. Streamlining IRB Review of Multi-site Studies

Questions 30-34: Requiring a single IRB of record for domestic multi-site studies may lead to efficiencies if implemented properly, as the use of a lead IRB would tend to decrease disparities among sites' implementation of protocols. This would: render IRB review and continuing review processes more rapid and efficient; increase predictability for researchers and subjects, all of whom would be operating under the same approved protocol and consent documents; and make more meaningful and accurate IRB review of adverse events and unanticipated problems in the course of a study, thus potentially better protecting the welfare of subjects.

Several questions and concerns, however, militate against the immediate adoption of a regulatory mandate for a central IRB. How would, for example, the lead IRB be selected to avoid forum-shopping by investigators? Depending upon how the lead IRB is chosen, there is a concern that there may be a "race to the bottom" in terms of IRB oversight. What regulatory

responsibilities, if any, would continue to be held by institutions and IRBs that had effectively ceded review to a central IRB? The responsibilities and attendant liabilities of these "ceding review" institutions and IRBs would need to be carefully considered and detailed in any OHRP proposal to require a single IRB of record for domestic multi-site studies. It is unclear at present how such a mandate could be implemented without dismantling or disrupting well-developed Human Research Protection Programs ("HRPPs") at local sites of a multi-site study. IRBs often act as the "hub of the wheel" or as a central control mechanism for an institution's HRPP. Harvard is concerned lest the immediate adoption of such a mandate degrade the research review process by eliminating from it meaningful site specific, local considerations and concerns.

Further, the central IRB proposal is both over- and under-inclusive, in that it regards all domestic sites as being sufficiently alike that a central IRB is appropriate, and regards all international sites as sufficiently dissimilar that a central IRB should not be similarly required. Neither scenario can be cast in such absolute terms. A central IRB, for example, may be more appropriate for a study sited in Boston and Amsterdam, than for a study sited in New York and rural Alabama or Alaska.

A full examination of these complex issues and the indirect effects of such a regulatory mandate is necessary before proceeding down this path. A federal funding program that has encouraged ceding of review among collaborating institutions is the Clinical and Translational Awards ("CTSA") program. There may be valuable lessons that can be learned from the way CTSA institutions have addressed these issues. For example, Harvard and its affiliated hospitals have developed a Common Reciprocal Institutional Review Board Reliance Authorization Agreement that may provide a useful framework for resolving the obstacles that

impede ceding review more broadly. We strongly believe that, at this time, a mandate of central IRB review for multi-site studies would predictably result in: (1) regulatory uncertainty and implementation gridlock: (2) likely failure of much central IRB review adequately to consider and accommodate critical local requirements and concerns; and (3) an aggregate reduction in protection of human subjects. Harvard believes, instead, that a more measured and careful process of encouraging central IRB use, accompanied in a step-wise way by OHRP issuance of guidance on critical issues attending central IRB review, would result in less disruption of the research enterprise, and eventually, improvements in a central IRB process that is anchored in deep collective experience.

Funders such as NIH, CDC, HRSA, non-HHS Common Rule agencies, and industrial sponsors all have it within their power, without a change in the Common Rule, to mandate use of central IRBs in multi-site studies that they fund. They should use that authority carefully, to drive the system toward the greater uniformity that is inherent in central IRB review. The FDA also has authority, if it is convinced that central IRB review is more effective at assuring protocol compliance and protecting subjects, to encourage industry to use central IRB review of multi-site studies submitted to support FDA applications. These steps can be taken now, would be meaningful ways to move toward increased central IRB use, and would more firmly establish an experiential basis for any future increase in central IRB use. This approach seems vastly preferable to the uniform mandate proposed in the ANPRM.

IV. Improving Informed Consent

A. Improving Informed Consent Forms

Questions 35-37: Prescribing by regulation any specific content or additional information to be included in consent forms may exacerbate the existing problem of excessively long and complex informed consent forms. There is no effective way to anticipate in "canned language" the sorts of information that must be in a consent form for any given study. Similarly, limitations on the acceptable length of various sections of a consent form will not necessarily make a consent form more comprehensible and may, in fact, make it less so in particular studies, by preventing the full exposition of specific issues and elements necessary to inform subjects adequately. Specific regulatory prohibitions or constraints also may contribute to the development of complex and largely incomprehensible consent forms.

Question 38: The focus instead should be on the appropriateness of the consent process and on methods to assure subjects' comprehension, i.e., improving IRB assessment of the sufficiency of the consent process, and improving researchers' capacity to engage subjects in the consent process. Guidance should encourage investigators to assess how well potential research subjects comprehend the information provided them before they are allowed to sign the consent form.

One change favored by Harvard that could provide more flexibility for the consent process would be to modify 45 CFR 46.117. Currently, §46.116 addresses the process of consent very briefly in the opening paragraph, and also provides the elements of consent. Section 46.117 addresses the consent form and obtaining signatures. We suggest changing the word "embodies" to "summarizes" or "reflects" in the following sentence: "A written consent document that *embodies* the elements of informed consent required by §46.116 ...." This

would provide IRBs with the discretion to make the written consent form a shorter, more useful document.

Additionally, consent in other cultural settings should be addressed, particularly for international research, in which community consent and other cultural requirements may be need to be respected. Harvard investigators have a long history of engaging in international research and working in many distinct cultural settings. In these settings, it may be appropriate to have less emphasis on signed consent forms as the only valid form of documentation. Waiver of signature should be explicitly allowed for research even above minimal risk if ethically and culturally appropriate.

B. General Consent for Future Research Use of Data and Biospecimens

Questions 45-53: The ANPRM proposals relating to future use of data and biospecimens contemplate some significant changes to the ways in which data and biospecimens would be collected and used for research purposes.

Harvard is mindful that there has been some public concern over unconsented future uses of personal data and biospecimens, driven by recent publicity about the cell lines derived from biospecimens obtained from Henrietta Lacks and biospecimens obtained from the small Havasupai tribe. The issues raised by these two cases, however, require careful identification and analysis. They may not, in fact, be identical to the concerns expressed in the ANPRM, and may not have been prevented by the regulatory solutions suggested.[3] In any case, Harvard

[3] In the case of Henrietta Lacks, the HeLa cell line derived was not entirely disassociated from the patient from whom the original cells had been obtained, as evidenced by the cell line's own name. This is a patent failure of researchers applying the process of de-identification or anonymization, the remedy for which might be to specify more carefully the process of de-identification, and penalize, even criminalize, any attempt to re-identify a biospecimen or data. Similarly, in the Havasupai case, various later research uses of subjects' biospecimens were allowed by IRBs under waivers of informed consent; but the targeted remedy for this may not be the elimination of

certainly agrees that the public deserves more sustained education and broader knowledge about future research and development uses of their personal data and biospecimens, about how those uses occur and under what circumstances, and about the essential advances in science, medicine and public health that have been facilitated by these uses. This could be done through, for example, additional information given to patients and others when receiving services during which these data and biospecimens are collected, and through modules added to informed consent processes for research. OHRP, FDA, CDC and other agencies similarly could orient public service messages to convey this information, stressing, for example, the public health value in ascertaining the time at which HIV entered the U.S. population, through research use of banked biospecimens originally collected for hepatitis B; development of tests to predict response to breast cancer therapies; isolation of the 1918 flu virus; and the identification of *helicobacter pylori* as a cause of gastric ulcers, which has also been linked to discoveries regarding the development of stomach cancer. The discoveries outlined above, and many more, were made possible by the research use of previously existing pathology collections for which it would have been impossible to obtain consent.

Harvard prefers an approach that stresses public education about the process and value of these future research uses of data and biospecimens, tightens IRB analysis of potential individual and group harms from the waiver of informed consent for research, and includes specific measures that would penalize, including criminally, researchers and others who would attempt to re-identify subjects through use of their personal data and biospecimens.[4] Harvard prefers this targeted approach over the approach to these issues suggested in the ANPRM,

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the waiver process, but instead the refinement of it, so that IRBs more closely analyze possible harms to subjects – and to discrete and insular populations such as the Havasupai – in any specific study for which consent is waived.

[4] At the same time, Harvard believes that there must remain some opportunity for re-identification in compelling cases, but these could be adjudicated by IRBs, through a waiver-like process, with clearly articulated standards.

which, by comparison, seems less targeted, less workable and less protective of subjects and the overarching public good.

Deficiencies Inherent in Standardized General Consent for Future Research Uses

Generalized consent to the use of biological specimens may be appropriate in certain circumstances and IRBs should be given the authority in the regulations to approve such consents. However, we think it unwise to make this form of consent the default mode for the donation of biospecimens and related information to research. Harvard is concerned that general consents would not necessarily contribute to the protection of research subjects and may, in fact, afford less protection than the current system of obtaining specific consent at time of donation, setting forth in that consent the presently known range of future uses, and being able to apply to IRBs for waiver of informed consent before undertaking specific future research projects. There are many circumstances where a general consent cannot predict the full range of research uses that may come into existence in the future.

In addition, the proposal would increase rather than decrease administrative burden and complexity of management of specimens. If prospective research consent were required for use of clinical biospecimens for all future research, hospitals, outpatient clinics, and educational and social service providers would have to adopt new research-consent infrastructures in the patient or client service setting. A number of processes would be needed within individual institutions, schools, agencies or health care systems to guarantee a point of contact for each type of patient (e.g., blood donor at blood bank, patient undergoing laboratory test, in-patient surgery patient, outpatient having biopsy or procedure at clinic, client receiving an addiction treatment service, a client with AIDS receiving a social service, etc.), in order to assure that the appropriate consents for future use are obtained. Clinical staff at each entry point would need appropriate

training in obtaining research consent at a time when such staff is principally responsible for assisting patients or clients before their clinical tests, procedures or interviews. Alternatively, if the main point of contact were instead an administrative office, such as registration, these clerical staff would be even less connected to the clinical and client service procedures, not to mention to any downstream research potential.

Accordingly, this consent proposal, as applied to data and biospecimens obtained during standard care or standard educational or social service delivery, but for which there may be a need for use in future research, would require a major shift in the research consent process from the research setting to clinical, educational or even clerical settings; this runs counter to the intent to create a meaningful consent process for future use of identifiable data and clinical biospecimens in research. The non-research, clinical service that would be charged with obtaining consent likely would have little understanding of the research enterprise and could in fact be completely disconnected from it. Patients or clients with questions about the research would not be able to get answers at the point of contact, and if every patient with a question were referred to a central number or other research office for follow-up, it is likely that many consent forms simply would not be returned, thus depriving future researchers of valuable resources.

Requiring through regulation a list of opt-outs that should be included in such general consent forms would not alleviate the deficiencies associated with a general consent and again would add to administrative burden and complexity. While this method may be one that some researchers would be willing to employ (it may be a good method for longitudinal studies where researchers expect long term contact with subjects), it is not suitable for all research studies. Even with opt out provisions there would still be questions raised in the future as to the

appropriate use of a biospecimen. Suppose an individual signed a general consent, but opted out of having his tissue used in a couple of known research modalities. Later the individual dies. How would one determine whether that individual's tissue may be used for a research purpose that was not even contemplated at the time of consent?

Adopting this proposal, under which general consents and their "opt-out" provisions would be binding on subsequent researchers and institutions, would impose an enormous and entirely predictable new compliance cost on health care, educational and public benefits systems that are already under significant financial stress. It would be difficult, and in many cases impossible, for researchers and institutions efficiently and cost-effectively to track such consents and related opt-outs (including opt-outs added by the subjects themselves) over time and across multiple institutions, communities, states and even countries. Even the cost of routinely gaining such general consents in the course of regular clinical care or other service delivery would be daunting.

The question of whether to include opt-outs in a general consent and determinations as to how to interpret the appropriate research uses of biospecimens would be much better left, as it is now, to the discretion of IRBs in the waiver of informed consent process. Otherwise, the process may predictably become gridlocked, as researchers, institutions and IRBs try to gain future consents from all patients and consumers, track those consents, find missing subjects, and analyze the inevitable ambiguities in these general consents and their opt-out provisions.

The Potential Loss of Valuable Research Materials

The aspect of the ANPRM proposal that varies most significantly from current practice of research review and approval is the essential elimination[5] of the waiver of informed consent option, by which a researcher now may apply to an IRB for a specific research use of existing identified data, or of existing identified biospecimens, if there is no ascertainable original general consent by the subject for such unspecified future research uses. Thus, in the absence of a general informed consent for unlimited future uses (which presumably would have to be obtained at the point of initial contact with the research subject), it would not be possible for a researcher later to use or re-use any previously collected identified biospecimens or any previously collected identified data for a new study, because the possibility of gaining a waiver of informed consent from an IRB would have been eliminated. Further, as described more fully below, in the absence of a general consent for future research use, it is not clear from the proposals how institutions should track biospecimens previously collected. Under the current regulatory structure, the inability of researchers to offer accurate information about future

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[5] There is some suggestion in the ANPRM (p. 44520, first column) that some form of waiver process might be preserved. Yet in a revised regulatory structure, the ability of researchers to gain a waiver would be fundamentally inconsistent with suggestions in the text of the ANPRM that future research uses are contingent upon their having been described, and consented to, in an original consent form. A waiver process would also be inconsistent with the ANPRM's assertion that subjects must have the ability to "opt out" of future research uses, with study enrollment never conditioned on an "opt in" to future uses; and that any "opt out" must be respected.

Specifically, the ANPRM states:

> [I]mportantly, this standardized general consent form would permit the subject to say no to all future research. In addition, there are likely to be a handful of special categories of research with biospecimens that, given the unique concerns they might raise for a significant segment of the public, would be dealt with by check-off boxes allowing subjects to separately say yes or no to that particular type of research (*e.g.*, perhaps creating a cell line, or reproductive research). Participation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using biospecimen. (p. 44519-44520).

As set forth more fully in the text, it is Harvard's position that the regulatory system should preserve the potential for a waiver of consent in cases where the specific future use offers significant research promise or is a matter of public health urgency, and the risk to subjects would be minimal.

unknown studies, and the inability of subjects to understand them, is accommodated by the waiver of informed consent process. Under that process, IRBs are trusted to consider specific future uses measured against the criteria for waiver. The waiver of consent process allows for IRB involvement and a thoughtful, considered approach to weighing risks, benefits, practicability, options, and the overall welfare of human subjects. The process requires a real-time analysis, based in present facts, of the risks and benefits of proposed research, without requiring researchers invariably to seek out past research subjects and (where possible) obtain new consent from them. Instead, appropriately, IRBs under the current regulatory regime require re-consent only when practicable and when the risk exceeds a minimal level. We trust IRBs to make these decisions every day relating to interventional studies in which there can be immediate and substantial risks to subjects; the waiver of informed consent, available only in minimal risk situations, is much less concerning in regard to risk to subjects than most other matters on which we routinely rely on IRBs' judgment.

The waiver process has, on the whole, worked well over the past two or three decades. Harvard believes that this mechanism of an IRB's analyzing waiver applications, which can result either in waiver, or in a direction to researchers to seek new, specific informed consent for new studies, is a more reliable protection for subjects than acquiring from them a general consent of unknown and unknowable breadth. As currently practiced, the waiver of informed consent process is, Harvard believes, a far more protective and preferable approach than the ANPRM proposal that would require a standardized general consent for the research use of any biospecimens (research or non-research in derivation) and data (of research derivation). Rather than seeking to implement a new process that is potentially hugely burdensome and that by its nature is unable to anticipate the extent of future research uses and inform subjects accurately

about those uses, the existing waiver of consent process should be retained, and as necessary, improved.

The new proposal would also eliminate the possibility that researchers could de-identify existing biospecimens (of research and non-research in derivation) and data (of research derivation), shedding subjects' identities, and then use the resulting de-identified materials for later research. The proposal adopts this approach ostensibly to protect subjects from the risks of re-identification of biospecimens and consequent compromises of their privacy. This, however, seems inconsistent with the approach adopted almost a decade ago by OCR in its HIPAA privacy regulations, in which de-identification of data (including those data associated with biospecimens) allows researchers, commercial agents, and anyone, to use those de-identified data in any way they see fit, for commerce, profit, and sharing with others. Admittedly, HIPAA is different in some respects because it regulates a very specific type of data, namely, individually identifiable health information in certain types of entities. Yet HIPAA privacy rules, with their plenary permission for health care providers and others to use de-identified patient data for any legitimate purpose, was deemed acceptable despite the context of a fiduciary relationship of the physician (or other provider) and the patient. If de-identification and free use of all resulting data for any purpose were allowed in that setting, there would seem no compelling reason why it should not be allowed in the research setting. Yet rejecting the HIPAA approach that de-identification of data takes the data outside of the regulatory scope, the ANPRM adopts a different approach when those data are used for research by entities covered by the Common Rule. This disharmony of approach between HIPAA in the health care delivery setting and the ANPRM proposal in the research setting seems unwise and imprudent, particularly when the potential impact on important research is

considered. Further consideration should be given to balancing the immense value of de-identified data to the research community and the need to preserve public trust in the research enterprise, particularly among individuals who have agreed to participate in specific research and have allowed their data to be used for that purpose.

The proposal would treat de-identification of biospecimens in this way because, it is thought, the source of any human tissue can now be identified if a third party is able to obtain and analyze other tissue from the same human, making all biospecimens inherently and presumptively identifiable. Yet this is true of data as well, in that a third party with ill intent could also seek to match de-identified data with data points derived from other data sets, thus ascertaining the identity of the person from whom the data were collected. The issues and risks are largely the same, although, given the plethora of publicly available data and the relative paucity of publicly available biospecimens, it is more likely that harm to subjects through re-identification would be done through data matches than through matches of biospecimens. Yet, as set forth above, we have made a social decision, not less than a decade ago, to allow HIPAA covered entities freely to de-identify data and then use it for a variety of purposes. For these reasons, the rationale for the proposal's stricter standards for future research uses of biospecimens seems weak.

Further, we note that HHS recognizes the benefits of research with biospecimens and throughout the ANPRM explicitly attempts to strike a balance between enabling such research to take place and protecting human subjects through streamlined consent requirements. The automatic default position that all biospecimens – regardless of the data collected with them – are identifiable seems to run counter to the flexibility that HHS is trying to build into other aspects of the ANPRM. Before adopting this approach, HHS should carefully consider

whether, as Harvard believes, such an inflexible position would severely limit the research utility of tissue and other collections.

Without a waiver of informed consent process, and without the possibility of de-identifying biospecimens and data so that no identified human subjects are involved, the only other option for researchers who wish to pursue new, unanticipated uses would be to attempt to re-consent donors through direct contact with them. This need to re-contact would – like the need to track opt-ins and opt-outs of the ANPRM's general consent – necessitate the creation of a system for identifying and tracking prior donors, an extraordinarily expensive, time-consuming undertaking that would, ipso facto, entail additional private health information risks. It would also lead to the loss of the use of biospecimens and data from subjects who cannot be found. The loss of data from subjects who cannot be found can create bias in data sets leading to erroneous conclusions in clinical research and incorrect findings based on incomplete data that may result in patient harm.

If current proposals relating to general consent for future research uses are adopted, OHRP presumably would, as suggested in the ANPRM, consider "grandfathering" existing biospecimens to exempt them from the new consent requirements proposed by the ANPRM, as applying the new consent rules retroactively would negatively impact the conduct of critical research. Harvard endorses this aspect of the proposal. Applying the new consent rules retroactively would effectively eliminate any possibility of using a very large set of data and biospecimens collected prior to the adoption of such new measures. Biospecimens and data collected over years of study have contributed to the development of a valuable public resource from which scientific discovery has advanced to provide immeasurable public benefit. The data and tissues included in these vast research repositories were collected under regimes that did

not require such broad consents for later research use. Applying these new consent rules retroactively would threaten this resource upon which researchers, and new scientific discoveries, rely so heavily.

HHS should also consider establishing a procedure to allow for the research use of biospecimens and data collected in foreign jurisdictions, where the details and complexities of these rules, as proposed, would likely not be known or not be consistent.

In summary, Harvard strongly disfavors the narrow approach of allowing future research uses of data and biospecimens only when there is a "general consent for future research uses," as set forth in the ANPRM. We believe it to be inefficient and unworkable in practice. We also believe this proposed approach would result in a net reduction in protection of subjects, and would have a substantial negative effect on public welfare, which has benefited enormously from past research that would no longer be allowed under this proposal. Instead, as described earlier, Harvard endorses alternative measures that would increase public awareness of the breadth of research uses of biospecimens and personal data, and that would directly penalize, and thus deter, any re-identification of subjects by use in research of their data or biospecimens.

ANPRM's Conflict with the Belmont Principles

Harvard notes that there are three values of equal importance that animate the Belmont Principles: respect for persons, beneficence, and justice. In seeking a situation in which every subject has consented to every use, even if in general terms, or has opted out of a use and had that opt-out respected, the ANPRM proposal seems to suggest, in a theoretical sense, that respect for persons invariably trumps beneficence and justice.

Beneficence in this case lies in the obligation that all of us have, one to the other, to participate in activities that benefit all of humanity. Harvard maintains that individuals should not undergo, without consent, research on their data and tissues that may cause harm to them. Instead, Harvard believes that there should be more exacting, more protective standards on the waiver of informed consent process, and measures to penalize attempts to re-identify subjects through their data and biospecimens; and Harvard offers these as measures through which the massive public value of the research uses of data and biospecimens can be preserved, for the good of all.

Concerns for justice arise when one considers whether allowing future research uses without subject consent somehow unfairly allocates burdens and risks. Given the widespread nature of the research uses of such substantial amounts of data and biospecimens, and their wide and diffuse benefit to the public good, it is difficult to argue that one social group has been harmed or preferred in place of another under the current regulatory structure.

It seems, on the other hand, contrary to the principles of beneficence and justice as put forth in the Belmont Report to advocate a state of affairs in which persons who decline to provide broad consent for all future use of their own data and biospecimens, even when risk to them is negligible, may nevertheless benefit from such research by depending upon the beneficence of others. In this sense, those persons who "opt out" are "free riders" who benefit from the beneficence of others but who refuse themselves to contribute. Further, if opt outs are allowed, one cannot then ensure that the results of research will be representative and not inherently biased or skewed.

As indicated above, Harvard agrees that there is a need for greater transparency in these research processes. The public may be relatively unaware that such research is occurring ubiquitously. Education should focus on why persons should want to support research using de-identified human materials both for themselves, for their families, and for society at large. Without such education, media attention (both positive and negative) may leave the public feeling that its rights were disregarded and its trust was violated. Members of the public should have the right to know how their data (information or biospecimens) were used. The importance of trust in the research enterprise cannot be overstated.

Potential Impact on Stem Cell Research

None of the proposed revisions in the ANPRM addresses stem cell research specifically, but certain proposals contemplate some significant changes to the way in which such research is conducted. Harvard has a long history in the conduct of stem cell research. Being an early adopter of the science, Harvard early on took pains to address the ethical oversight of such research. Prior to, and concurrent with, the issuance of the National Academies' Guidelines for stem cell research, Harvard researchers and research administrators convened panels of experts and ethicists to consider issues related to this area of research; conducted symposia to examine the scientific and ethical contours of emerging developments in this area of research; and participated on advisory committees to policy-making bodies. The following comments are a result of Harvard's significant experience in this area, as developed over years and in response to fluctuating state and federal policies and evolving national and international ethical guidance.

Under current rules, in most cases (and always in the case of human embryonic stem cell ("hESC") research) study subjects must provide written informed consent to donate biospecimens (such as embryos) for research, but the informed consent document must describe

the study with some specificity. If researchers intend to register hESC lines with the NIH, the consent forms must inform donors about many specific aspects of a study, including, for example, that the donated embryos will be destroyed as part of the research. Also under current rules, in situations in which a researcher is interested in using a biospecimen for later, "follow-on" research that may not have been contemplated at the time of collection, the Common Rule allows for the researcher to apply to an IRB for a waiver of informed consent to allow for the new use without having to re-consent study subjects. Assuming the proposed new use meets certain requirements set forth in the current version of the Common Rule, such as that the new study is of minimal risk to subjects, the IRB could waive the necessity of obtaining a new written consent.

The proposed rules would still require written consent for the research use of biospecimens, but the consent would not need to be study-specific, and could be very general and allow for open-ended future research. Moreover, under the proposed rules, the option for a researcher to apply to an IRB for a waiver of informed consent would effectively[6] be eliminated.

The proposal to require the use of a standardized general consent for the future research use of biospecimens and the effective elimination of the waiver of informed consent raises specific concerns for hESC researchers. It may never be possible for consent forms for the donation of embryos to be in the form of the "general consents" that HHS is envisioning in this proposal. It is difficult to believe that either state or federal authorities, or medical ethics bodies such as the National Academies of Science ("NAS"), would condone the donation of embryos to research under general, non-study specific consent forms that allow for "open-ended" future

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[6] See footnote 5.

research.[7] Certainly, current NAS[8] and National Institutes of Health Guidelines on Human Stem Cell Research ("NIH Guidelines")[9] would not permit this. The NIH Guidelines were promulgated just over two years ago and they include specific and detailed informed consent requirements that are unlike any other federal requirements for the donation of biospecimens to research in their specificity. It is also doubtful that an institution's IRB and ESCRO committee would permit research to be conducted in this area based upon a "general consent for future research" as proposed in the ANPRM. Further, even if all external and institutional regulators and officials were to allow this, one doubts whether there would continue to be sufficient (or any) donors willing to donate embryos under circumstances in which the research is not defined and complete latitude is given to researchers for later use. We are apprehensive that future research might be greatly curtailed if, for legal, ethical and practical reasons (such as donor preference), hESC consent forms for donation of embryos continue to be specific, but fail to predict (as they easily might) future research uses whose contours are unknown, given that, under the ANPRM proposal, the waiver of informed consent process would no longer be available to researchers.

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[7] One could imagine that if the federal government actually decided it would allow this in the case of embryo donation, this might trigger a new round of state legislation enacting protections for donors, just as states were spurred to action to regulate this area of research when the federal government decided, under the Bush policy, to absent itself from regulation of this area of research.

[8] According to Section 3.2 of the NAS Guidelines:

> Consent for donation should be obtained from each donor at the time of donation. Even people who have given prior indication of their intent to donate to research any blastocysts and/or morulae that remain after clinical care should nonetheless give informed consent at the time of donation.

Additionally, Section 3.6 of the 2010 NAS Guidelines outlines 11 specific disclosures that must be made during the informed consent process.

[9] The 2009 NIH Guidelines on Human Stem Cell Research also require consent at the time of donation, regardless of whether the donor provided prior indication of their intent to donate, and require a number of spcific disclosures in conjunction with a donation to human embryonic stem cell research.

Additionally, the proposal to require that consent forms include provisions for study subjects to "opt out" of specific research uses, or allow research subjects to add their own "opt-outs," would place burdensome constraints upon stem cell researchers. The predictable effect of such a proposal would be to create a web of administrative complexity that would compel the need for costly tracking systems for opt-out preferences, without measurable benefit. We are troubled that the proposal appears to disallow the strategy of limiting enrollment in a study to those individuals who agree to the entire program of intended use, which is the option many institutions have used with stem cell research, and which is the least burdensome in terms of long term use of materials.

Beyond the specific issue raised above, the ANPRM proposal also raises questions such as how the proposed rule will harmonize with the specific informed consent requirements of the NIH stem cell funding guidelines; whether the opt out provisions would apply to derivatives of the donated material (e.g., induced pluripotent stem cell ("iPSC") lines and non-living material derived from the original biospecimen (e.g., DNA and RNA); and how long must one honor opt outs. (Stem cell lines are immortal, and will be useful in research long after donors have died. Will a consent form opt-out be binding in perpetuity?)

HHS should consider (and any NPRM should clarify) how this proposal might affect other applicable stem cell research consent requirements, such as the NIH Guidelines, as well as the effects of applying such a rule retrospectively and to biospecimens donated in foreign jurisdictions. The NIH Guidelines provide an excellent model for the treatment of the latter. In addition to providing new and detailed consent requirements, the NIH Guidelines also include a process for recognizing the validity of donations that pre-dated the effective date of the Guidelines and hESCs derived in foreign jurisdictions. The NIH Guidelines outline an

alternative process of review by a NIH working group to "enable pre-existing hESCs derived in a responsible manner to be eligible for use in NIH funded research." Similarly, the NIH Guidelines allow for the use of hESCs derived in other countries in NIH-funded research in which the donation was subject to standards "at least equivalent" to those provided for in the guidelines.

Summary of Recommendations Relating to "Future Research Use"

In summary, Harvard believes that an approach more attainable, more practical and more protective for research subjects than that set forth in the ANPRM would include the following:

- Public education about the process and value of these future research uses of data and biospecimens, including national governmental efforts and efforts of individual researchers, research institutions, and professional societies, so that the social value of future research uses can be more widely understood;

- Education by health and social service providers of patients and clients as to the practice, protections, and promise of future research uses of their data and biospecimens gained in non-research settings;

- Adoption of Common Rule standards that promote a more rigorous IRB analysis of potential individual and group harms from the waiver of informed consent for research, including protections for discrete or insular communities whose individual members may be directly affected by use of even de-identified or anonymized data and/or biospecimens;

- Legislative efforts to penalize, including criminally, researchers and others who would attempt to re-identify subjects through use of their personal data and biospecimens;[10] and

- Issuance of federal guidance about the binding commitments that researchers and research institutions make when they promise subjects that personal data and/or biospecimens will be used "only" or "exclusively," or will not be used at all, for specific future research purposes.

[10] At the same time, Harvard believes that there must remain some opportunity for re-identification in compelling cases, but these could be adjudicated by IRBs, through a waiver-like process, with clearly articulated standards.

V. Strengthening Data Protections to Minimize Information Risks

The ANPRM seeks to relieve burdens on IRBs and investigators for studies in which the primary risks are informational in nature by proposing to adopt the HIPAA standards for personally identifiable data, de-identified data and a limited data set. The proposal further would institute new data security standards modeled after the HIPAA Security Rule for research involving identifiable data or limited data sets. While Harvard agrees that it would be useful to create uniform standards in this area, a wholesale regulatory adoption of HIPAA raises several concerns, as described in the subsections below and in Harvard's answers in this section to the specific questions raised by the ANPRM.

Harvard applauds the specific attention given to informational risks in the ANPRM. Informational risks have consequences, methods of evaluation, and methods of abatement different than other types of potential harms from research, and addressing these specifically will improve the management of informational risks. However, Harvard disagrees with the suggestion that, "Standardized data protections, rather than IRB review, may be a more effective way to minimize informational risks."[11]

Informational risk, like any risk, is a function of the probability and magnitude of the harm. The overall level of risk to research subjects imposed by research use of data is a function both of the content of the data (including the variables included and the characteristics of the sample or population covered by the dataset) and the controls established on access to the data (technical and institutional). While Harvard understands the necessity of separating these elements in the drafting of the ANPRM, nonetheless a framework is needed for identifying

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[11] Fed. Reg. at 44516.

intersections of these two elements that correspond to levels of risk acceptable at the various levels of review that might be established in a revised Common Rule.

Specialized expertise is required for evaluation of informational risks. IRBs are well qualified to weigh the magnitude of harm associated with the inadvertent release of a particular set of information concerning a subset of participants. For example, IRBs routinely consider the consequences of potential information breaches in determining whether a study is eligible for expedited review.[12] On the other hand, most IRBs tend not to possess the expertise needed to mitigate risk of a data breach by technical and operational measures. This is more properly the domain of institutional information security officers (who in turn lack the IRB's experience in looking at a protocol to calibrate the impact on participants of a loss of the identifiable data involved in the study). Accordingly, some structures must be developed to facilitate review of informational risk by both IRBs and an institution's information technology personnel.

Institutions should be afforded the discretion to develop their own policies for facilitating the participation of IRBs, researchers and information technology personnel to ensure that research data security measures commensurate with the data security risk of a particular study are developed and implemented. Institutions that house IRBs already have the resources to carry out this task, because they are already managing information security risks: hospitals manage patient data, and universities manage sensitive student data. For example, Harvard developed a Research Data Security Policy, http://www.security.harvard.edu/harvard-research-data-security-policy-protection-memo, that sets out the respective roles and responsibilities of IRBs,

[12] "The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal." Common Rule, 45 CFR 46.110.

researchers and Security Information Officers, as well as a process to ensure that technological and operational measures appropriate to the information risk posed are in place before IRB approval is granted for research involving identifiable information. Currently, the Common Rule directs IRBs to ensure data security. OHRP could support the efforts of institutions through consultation and guidance, rather than through imposition of a new regime modeled on HIPAA, as envisioned by the ANPRM.

Human studies certification should include training requirements with adequate instruction on the nature of informational risks and the rationale for and content of rules governing management of restricted data. Appropriate training and education should be bolstered by oversight procedures including audits and penalties. Sanctions should be established for improper disclosure of data subject to restrictions, particularly when done for pecuniary gain or with disregard for potential harms to research subjects (particularly when this occurs after receipt of training and information about restrictions on the dataset).

Any revision of the Common Rule should also be cognizant of requirements imposed on researchers by funding agencies for release of public-use versions of research data, and should include suitable provisions to ensure that these requirements do not conflict with appropriate Common Rule nondisclosure obligations.

A. Characterizing Information with Respect to Potential for Identification

Question 54: Harvard notes that the HIPAA Privacy Rule is directed in the first instance at the Covered Entity that is the provider of the data, while the Common Rule is directed at the researcher who may be the recipient of data from a HIPAA Covered Entity.

Thus the changes suggested by the ANPRM involve substantial changes even for researchers using HIPAA-covered data.

The ANPRM proposal to shift from the Common Rule approach to determining what is "identifiable" to an adoption of the HIPAA Privacy Rule may indirectly increase burdens on IRBs and the research community. The Common Rule approach considers information not to be identifiable if the subject's identity is not "readily ascertainable" by the investigators conducting the research. Alternatively, the HIPAA Privacy Rule has a considerably stricter standard for de-identification, requiring either (i) the removal of 18 specified identifiers (of the individual as well as the individual's relatives, household members, and employers), along with the lack of actual knowledge that the remaining information could be used to identify the individual; or (ii) a formal determination by a qualified expert in statistics that the risk of identification is very small. Applying the HIPAA standard would invariably expand the scope of what is considered to be individually identifiable and, consequently, would expand the scope of what is considered to be human subjects research under the Common Rule. This could, in turn, increase the burden on IRBs, by increasing the circumstances under which informed consent and IRB approval are required.

Harvard is also concerned that this shift would also prove overly burdensome as applied to social and behavioral research. HIPAA, as originally conceived, was intended to apply to Protected Health Information ("PHI") in the clinical care setting. Even in the clinical research setting, HIPAA's structured approach leaves little flexibility for IRBs to calibrate review based on likelihood or magnitude of the harms. Accordingly, there has been criticism for several years that the rigidity of these standards does not translate well into the clinical research context, where it currently applies. Extending strict definitions and protections that were designed primarily for

the clinical care setting to the non-clinical research setting will be even more problematic. Indeed, extending HIPAA standards to all social, behavioral and educational research will work counter to efforts in other areas of the ANPRM to decrease burden and exclude these same areas of research, many of which are minimal risk.

Even if IRBs do not possess technical skills in assessing the risk of disclosure, they are qualified to assess the potential harm to research subjects of disclosure (that is, the sensitivity) of particular data elements, and it is reasonable to include assessing such sensitivity within an IRB's scope of review.

Question 55: Harvard strongly supports the principle that de-identification standards should be re-examined and regularly updated to remain current with developments that affect informational risk, such as availability of new external sources of data, advances in computing methods (e.g., cloud computing), and research findings that support reassessment of risk. A suitable mechanism for such a review might consist of a committee of experts from within and outside federal government, and a staff equipped to support the committee's work and to receive confidential communications concerning incidents of informational harms. Suitable channels of communication should be established to facilitate rapid communication of changes in standards to researchers, consulting experts, and relevant institutions.

B. Standards for Data Security and Information Protection

Even if most breaches of data security are due to lapses in basic computer security and systems management, controlling these lapses involves training of staff who have access to data and establishment of appropriate procedures for data management. The emphasis on technical aspects of computer security seems somewhat one-sided, when in fact these lapses

most frequently involve human errors such as carrying data on unsecured media, sharing passwords, or mixing sensitive identifiable data with otherwise insensitive data in analytical files.

Further, retrospective audits may not be a suitable mechanism for enforcing data security across the many institutions and research groups that are involved in covered research. It is unclear who would conduct these audits, and what number of them would be feasible within available resources. Implementation of data security requirements might be best conducted by relying on the institutions sponsoring research, working through their own appropriate sub-units. For example, an institution might establish its own standards for system management and training for groups (departments, labs, or research teams) handling data at various levels of sensitivity. It could then certify such groups as having established adequate safeguards to handle data up to a certain level of sensitivity. External audit could then focus on the adequacy of the institutional procedures, rather than on the individual research projects. (Question 66 seems to assume this approach although this is not explicit in the narrative text.)

Question 58: Any potential new data security and information protection standards should only apply prospectively to data and biospecimens collected after the implementation of the new rules.

Question 59: The HIPAA Rules are primarily designed to assure the security of data being transmitted for health care treatment and operations. While the rules specify the categories of data that might be released from the health care system to researchers, it does not deal systematically with how those data are protected once they are released. Rules designed for operational data management will not necessarily translate well to the much different and more

diverse world of research. The relevant categories for establishment of data security standards involve the sensitivity of the data, not whether the data is health data.

Question 60: General guidance and standards for data security should address the special issues arising during field collection of sensitive data, during which some controls applicable to analytic data files are not feasible and identifying information may inevitably be linked to sensitive responses.

Question 61: The National Institute of Standards and Technology ("NIST") standards, designed for the types of systems used in federal government, are too prescriptive to be generally applicable across the more diverse information technology environments that exist across the non-federal research enterprise. A system of levels of data security should be defined in more general terms, focusing on requirements rather than specific procedures. A process should be established through which institutions could develop their own data security plans consistent with these requirements. Voluntary development and dissemination of a few standardized plans appropriate to the resources of various research centers should be encouraged.

Question 62: Data Use Agreements (DUAs) are an important tool for ensuring compliance with data protection standards. Limited data sets carry some risk of re-identification and the use of a DUA provides a flexible mechanism for controlling the risk of re-identification by controlling not only the limited data set and who has access but also other data files that may be used in the research project. Training of researchers is another important tool for ensuring compliance with data protection standards. Both approaches can be used in combination to provide access to higher quality data than simply relying on technical means alone.

Question 63: A prohibition against re-identifying de-identified data would be a reasonable requirement. This recommendation is consistent with Harvard's recommendation above, that criminal and civil penalties associated with re-identification of de-identified biospecimens would represent a more effective and more efficient method of protecting persons whose information is used in research than treating all de-identified biospecimens as though they are, in fact, identified. Exceptions to a general prohibition on reidentification of de-identified datasets might be allowed to permit adding essential content to the dataset, to enable correlation of multiple datasets for legitimate research purposes, or to test the identifiability of datasets before sharing. Harvard believes that there must remain some opportunity for re-identification in compelling cases, but these could be adjudicated by IRBs, through a waiver-like process, with clearly articulated standards that would acknowledge both the potential risks to subjects and the value of the knowledge being sought. Additionally, Harvard is concerned that if reidentification even for valid purposes under oversight is prohibited or discouraged, there will be pressure not to de-identify, which will in turn increase the likelihood of harm should there be a security breach.

Question 64: The prohibition on re-identification and indeed any Common Rule protection against informational risk would be useless if the researcher is allowed to redistribute data to users who are not under Common Rule restrictions. Training will help ensure that researchers understand the limitations on redistribution.

Question 65: This seems like an appropriate safeguard for "excused" research on sensitive data, and could be linked to the institution's local procedures for assessing adequacy of data security. The registration should include updated contact information and re-certification of the terms and conditions on an annual basis.

Question 66: Institutions should be allowed the flexibility to assign oversight responsibility as part of their overall plan for human subjects research protection.

In sum, Harvard is concerned that the ANPRM proposals regarding the extension of HIPAA standards to all research under the Common Rule would be exceedingly difficult to implement, burdensome to the research community and generally excessive in relation to the benefits realized. Any proposed rule must ensure proportionality between the information risks and the data protections requirements.

VI. Data Collection to Enhance System Oversight

Questions 69-70: Creating a system for electronic reporting of adverse events to a central website for interventional protocols may be a useful tool for informing the public about the overall safety of research with human subjects, but it is less clear that requiring such reporting as it relates to social and behavioral research or requiring reporting of unanticipated problems would be as useful. Neither adverse events nor unanticipated problems are defined in the Common Rule, and thus there would be wide variability from one institution to the next in terms of what is reported. Additionally, unanticipated problems are often not likely to rise to a level of concern necessitating public disclosure. In fact, disclosing such problems without appropriate context may lead to greater confusion and public misperceptions about risks related to human subjects research.

VII. Extension of Federal Regulations

Question 71: As an institution that voluntarily applies the Common Rule precepts to all human subjects research, Harvard strongly supports the goal of making these protections more universal. Currently, several areas or types of research are not subject to the Common Rule

regulations, and such gaps in coverage of the Common Rule are undesirable. Examples include research in private medical and other health provider practices, dedicated research sites, or research in community hospital settings that does not involve an FDA-regulated product; much research with nutritional supplements; student projects at community colleges or smaller schools that do not traditionally conduct research as a major part of their mission; research funded by private foundations; and research funded by federal agencies that are not signatories to the Common Rule (e.g., National Endowment for the Humanities). While voluntary application of the regulations does occur in some cases, it is not required. Accordingly, a solution is needed to extend appropriate protections to all research subjects, without arbitrary limitations or gaps in coverage.

The ANPRM proposal to extend federal regulatory authority to encompass non-federally funded research, however, inappropriately focuses on academic institutions, fails to achieve the goal of applying the Common Rule precepts to all human subjects research, and raises particular concerns in the area of stem cell research and other politically controversial research. In this proposal, the ANPRM focuses on academic institutions that receive ***some*** federal funding, where the risk to subjects generally must be considered to be relatively low. Most academic institutions, like Harvard, voluntarily apply the precepts of the Common Rule to all research, even if they do not "check the box" to subject all their research to OHRP jurisdiction. In addition to its failure to target non-academic institutions where risks to subjects may be greatest, this proposed regulatory change also fails to encompass institutions that receive ***no*** federal funding.

For these reasons, the proposal set forth in the ANPRM would offer only a partial solution at best and would foster an environment in which investigators and sponsors would have motivation to seek out institutions that receive no federal funding (and are thus exempt from the Common Rule) and avoid those that do receive federal funding. Observers have even questioned whether institutions that receive few federal funds would now have motivation to avoid receipt of federal funds altogether, in order to make themselves more attractive to investigators and sponsors, or as a risk management strategy. The net result would be to impose additional requirements on those institutions that receive federal funding, while doing nothing to reach those currently operating outside the regulations.

Further, this proposal raises more questions than it resolves. If a smaller institution receives a single federal grant, thereby triggering extension of the Common Rule, does that obligation remain in perpetuity, or does it end with the end of funding and the close-out of a grant award? Also unclear is how this would apply to institutions that receive funding from federal agencies that have not themselves adopted the Common Rule. Further, as this proposed rule would represent an extension of federal executive authority through rule-making (as opposed to legislation), it may be particularly sensitive to legal challenges.

A more apt approach, and one that would target all human subjects research, including all non-federally funded research and research conducted outside of academic settings, would be to extend the Common Rule through legislative means.

With respect to embryonic stem cell research, and other potentially politically controversial research methodologies the federal government has chosen not to fund, whether through law, regulation, or guidance, there are compelling reasons to refrain from such an expansion of Common Rule jurisdiction. To expand OHRP jurisdiction in this way would create

an imbalance of authority in research oversight by arming federal administrations that may be hostile to a particular field of research with the ability to thwart progress those fields. Throughout history, various fields of research have emerged that have been politically controversial and have been sensitive to funding and policy shifts as policymakers achieve a comfort level with the science. The promising field of embryonic stem cell research is only the most recent example.[13] Although the conduct of embryonic stem cell research is not prohibited by federal law, the federal funding mechanism has been employed as a lever to limit such research substantially. The one constant surrounding federal funding of embryonic stem cell research through the years has been its variability, as such funding has been subject to funding bans, limiting executive orders and recently, judicial injunctions. Throughout this time of uncertainty for federally funded stem cell research, exceptional progress has been made in understanding the underpinnings of stem cell biology in ways that soon will likely translate to patient care. This progress has largely resulted from the support of private philanthropy. Expanding federal jurisdiction of the Common Rule may make legally, scientifically and ethically valid stem cell research conducted with private funds subject to selective future federal Common Rule enforcement based upon changing political dynamics and would threaten to cast the same shroud of uncertainty over privately-funded research that now attends federally-funded stem cell research.

An expansion of federal jurisdiction may also deter private sponsors from stepping in to fund research that is legally, scientifically and ethically valid, but that the federal government has made a decision not to fund. A private sponsor making the decision to fund basic research weighs many considerations. Foremost among these considerations is the potential for making a

[13] Another example involves research involving pregnant women. Certainly, some Part B restrictions seem to have little to do with protecting these subjects of this research and more to do with the politics surrounding abortion.

serious contribution to enhanced understanding of science and, thereby, contributing to some greater public benefit. Additionally, sponsors weigh the relevant costs associated with the research and the level of regulation to which it is, or may be, subject. When private sponsors are willing to fund research that the federal government is unable or unwilling to fund, it is unwise national research policy to deter them from doing so either by the threat or the possibility that such voluntarily-funded research might be subjected to broadened agency authority of the type generally associated only with the acceptance of federal funds.

Public and private funding of research are two vehicles of scientific discovery, both of which must be pursued in tandem to achieve progress. The research enterprise, by its very nature, pushes the boundaries of imagination and knowledge. In view of this, it is foreseeable that controversy will attach to certain new lines of research, making such research less attractive for the public funding vehicle. Where public funding of legal, ethically and scientifically valid research is unavailable due simply to the controversial nature of the research, wisely managed private funding of ethically conducted research should be encouraged. Applying the same oversight and reporting requirements that are now associated solely with the acceptance of federal funding to research conducted legally and ethically with private funding would run counter to this goal.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Questions 72-74: Harvard supports the proposal to promote consistency across federal agencies and departments regarding guidance on the protection of human subjects. Harvard researchers are involved in a wide range of research activities, and thus are subject to many different agencies' rules and guidance. Harmonization to the extent possible is a positive step, as it would promote predictability and thus facilitate compliance.

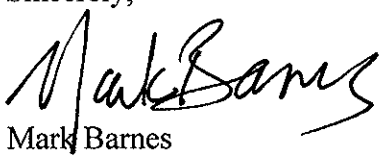
In particular, there is an urgent need to address and harmonize, to the extent possible, inconsistencies in interpretation and implementation across Common Rule agencies. Currently, there are inconsistencies among Common Rule agencies, borne of differing interpretations and/or differing levels of engagement. Examples of contradictory guidance include, for example, the definition and handling of protocol deviations, and whether recruitment activities are considered research. There is also a related need to address the enforcement of guidance, which varies by agency.

Where possible, it would be helpful to the research community for Common Rule agencies to issue common guidance. For example, the recent issuance of joint guidance by OHRP and FDA to clarify and revise their stance on exculpatory language in consent forms was extremely helpful, and this practice of shared, common guidance should be encouraged. By contrast, efforts by the same two agencies to address unanticipated problem reporting were blunted by the issuance of separate guidances on this topic. As a result, the research community, sponsors, and IRBs have struggled with the separate guidance that was ultimately issued.

Harvard appreciates the opportunity to participate in OHRP's efforts to modernize and revise the current regulations for protecting human subjects. We recognize the magnitude of the task before OHRP and HHS, and endorse the ultimate goals of this endeavor. We hope that our experience as an institution with a long history of engaging in the conduct and oversight of human subjects research activities might help to inform the Department's process.

We look forward to continuing to work with OHRP and HHS to improve protections for human subjects, while facilitating valuable research and reducing burden, delay and ambiguity for researchers.

Sincerely,



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