October 26, 2011

Jerry Menikoff, M.D., J.D.
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Comments on Advance Notice of Proposed Rulemaking entitled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators"- **Docket ID No. HHS-OPHS-2011-0005**

Dear Dr. Menikoff:

The Consortium of Independent Review Boards ("CIRB") is pleased to provide comments on the Department of Health and Human Services' ("DHHS" or "Department") advance notice of proposed rulemaking, which seeks input on how to modernize human subject protection regulations to make them more effective. See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, Advanced Notice of Proposed Rulemaking, 76 Fed. Reg. 44,512 (July 26, 2011) (hereafter, "ANPRM").

I. OVERVIEW

The current regulations known as the Common Rule or Subpart A, originally published in 1981, and again in 1991, are certainly of an age at which they should be re-considered in light of changes in the research environment, technology, and fresh concepts of privacy and of community and local conditions. Throughout the ANPRM, DHHS acknowledges that the rules are risk-based and are appropriate. However, the Department expresses concern that the application of these rules by some institutions is less than ideal, and CIRB cautions that in generalizing from the few to the many, the Department may be suggesting solutions that are more drastic than necessary to address the perceived problems with the current system. Simply updating current regulation or guidance is likely more useful than a complete regulatory overhaul.

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Currently, the primary places to learn about rules or best practices in human subject protection are the annual Public Responsibility in Medicine and Research meetings, the research community-sponsored and University of Pennsylvania-hosted list serve, *IRB Forum*, and publications like *IRB Advisor* (AHC Media) and *IRB Ethics and Human Research* (Hastings Center). Better methods of eliciting peer-to-peer guidance and identifying community standards may be viable, but these venues have been successful in assisting the community to bridge current ethical regulations with transformations in the research landscape.

The inquiry regarding the adequacy of human subject protections is taking place within the context of damaged public trust in research. The damage has resulted from sensationalized risk outcomes resulting from one or another critical area/omission, the occurrence of unforeseen harm, and/or the occurrence of a known potential harm.

It is appropriate to assess oversight mechanisms and whether better/different procedures would improve subject protection. Application of the current regulations across institutional review boards ("IRBs") from various organizations is indeed inconsistent. It seems that many of these differences stem from an unrealistic expectation of what is meant by the IRBs' "protection" of human subjects, which gives way to a muddled understanding of the purpose of IRB oversight within the research community and most certainly with the public.

The regulations state that the function of the IRB is to "protect" the rights and welfare of human subjects. That is accomplished by ensuring that human subjects' ethical rights and needs are provided for in the research situation. Yet risk is inherent in the research situation – both the risk of unforeseeable harm and the risk of occurrence of a known potential harm. The most rigorous IRB cannot "protect" a research subject from such occurrences. While the regulations recognize this fact in their criterion for IRB approval that "risks are minimized to the extent possible," too often, when research harm presents itself, this is viewed as a failure of oversight.

Further, the regulations describe a system of procedures and responsibilities of which the IRB is only part. It may be accurate to state that the operation of the entire system provides protection. It may even be accurate to identify particular parties within the system that are responsible for providing protection from harm. However, the system would benefit if we can restate the function of the IRB to clarify that its purpose within the system is to ensure that research is ethically justified, and stays that way for its duration.

CIRB's comments will address DHHS' seven proposals to modify the current regulatory framework in Sections II through VIII of this letter.[1] However, prior to addressing the ANPRM proposals, CIRB would like to identify some concerns and solutions that either raise broader issues or were not mentioned.

[1] While in many instances CIRB's comments address issues beyond those specific questions enumerated in the ANPRM, attached to this letter is an appendix cross referencing CIRB's comments on specific ANPRM questions.

First, the definition of "research" should be altered to eliminate reference to program evaluations and demonstration grants, the results of which are rarely generalizable beyond the specific program. See ANPRM Question 24, 76 Fed. Reg. at 44,521.

Second, CIRB recommends that DHHS assign the task of grant review to a party other than the IRB, for example, the funded institution. Currently, the Office for Human Research Protections ("OHRP") follows its predecessor organization's (Office for the Protection from Research Risks ("OPRR")) policy statement, interpreting 45 C.F.R. § 46.103 to require the IRB to review the grant application to assure that it is "entirely consistent with any corresponding protocol(s) submitted to the IRB." See OPRR Policy Statement entitled "IRB Review of Applications for HHS Support."[2] Grant proposals generally are quite lengthy, providing many details that go well beyond the purview of the IRB. Indeed, the clinical trials are usually the last and least defined of a number of specific aims in the proposal. Moreover, such applications require scientific peer review in a study section that is selected specifically for the grant area, and it should not be the IRBs' role to contravene the scientific review of the grant or to try to manage how the grantee spends the grant funds. Moving the grant review process away from the IRB can be accomplished through revision of this OPRR policy.

Third, while CIRB will address its support for harmonization of agency human subject protection regulations in Section VIII of this document, CIRB wants to emphasize that a vigorous commitment to harmonization is critical to enhancing human subject protections and reducing burdens on the research community.

Fourth, within the history of human subject protection there has been considerable condemnation of IRBs, their inconsistency and institutional mission creep, without adequate recognition of the forces that result in these differences. Over the years, both institutions and regulators, through mandate or enforcement, have required IRBs to undertake additional activities in addition to the core mission of reviewing research. This can give the appearance that some IRBs review research slower than other IRBs even while the actual review time remains unchanged but other tasks are being accomplished. Further, while there is significant attention on IRBs that fail to comply with regulations through the publication of Warning Letters or other notices of noncompliance, there is little acknowledgment or praise for the much larger majority of IRBs that comply with the regulations. Unfortunately, this ANPRM continues the history of negativity. There is condemnation of the institutions that over-review but little recognition of the vast number that use the rules as intended. CIRB suggests that another tool should be added to the regulatory agencies' toolbox of measures to assure compliant and ethical review. Specifically, public recognition of a job well done by an IRB could provide a model to other IRBs as to the regulatory agencies' expectations.

Fifth, there is no discussion or consideration of root causes. A root cause analysis of some of the mentioned problems might reveal far simpler solutions. Again, fear generated from years of determination letters without any public recognition of success could be largely responsible for over-review. Levels of trust and faith in government have largely eroded, leaving institutions to solve problems on their own. Not only does CIRB support a thorough root cause investigation, it

[2] *Available at* http://www.hhs.gov/ohrp/policy/aplrev.html.

offers a recommendation that should help address the over-review issue. Consistent with the intent of this ANPRM to focus on risk-based determinations, CIRB suggests that agency oversight, inspection activity, and findings also should be risk-based. Such an approach may allow the research community to be less distracted by administrative details, and to better attend to critical human subject protection functions. The Food and Drug Administration's ("FDA") draft guidance to sponsors describing risk-based approaches to monitoring appears to indicate that FDA is open to risk-based methods of review, and CIRB supports adoption and extension of this approach to agency activities. See FDA Guidance for Industry entitled "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring";[3] see also Morrison, BW et al. Monitoring the quality of conduct of clinical trials: a survey of current practices, *Clin Trials* 8: 342 (2011).

Finally, the ANPRM appears to reflect little evidence of coordination with other agencies. Although DHHS and FDA regulations are listed in the ANPRM, there is no discussion concerning the differences in mission, regulatory structure, or successes in other agencies.

II. ENSURING RISK-BASED PROTECTIONS

As the ANPRM explains, human subject protection regulations are currently risk-based with three recognized categories: exempt from review, expedited review, and review at convened meetings. This hierarchy has worked successfully in many institutions for many years. Nothing in the ANPRM suggests that the system is broken, only that some institutions have elected to use the system more stringently than critics would argue is necessary and that there is variability among institutions.

Over the years many institutions have elected to apply a standard to research that is stricter than set forth in the regulations. Using a reference from a 1984 article in *IRB*, DHHS states that, "many surveys that are unlikely to lead to any harm to subjects nonetheless undergo review by a convened IRB." See ANPRM 76 Fed. Reg. at 44,514, citing to Cann CI, et al. IRBs and epidemiological research: How inappropriate restrictions hamper studies. *IRB* 6(4):5-7 (1984). CIRB believes some historical context is necessary to understand this progression towards stricter standards.

OHRP guidance throughout the years has reinforced the right of institutions to elect to apply a standard higher than the regulatory minimum. OPRR Report Number 95-02 says that "institutions may elect to review all research under the auspices of the institution even if the research qualifies for exemption . . . ." See OPRR Report 95-02, Exempt Research and Research That May Undergo Expedited Review.[4] Accreditation standards, such as those set forth by the Association of Accredited Human Research Protection Programs ("AAHRPP") and ascribed to by a number of research organizations, are the direct result of DHHS policy advanced in the

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[3] *Available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

[4] *Available at* http://www.hhs.gov/ohrp/policy/hsdc95-02.html.

early 2000's. AAHRPP promotes the concept of the human subject protection program within which the IRB works with excellent rather than baseline standards. Thus, that we now find a number of institutions applying a higher standard than the baseline should be seen as an expected outcome of government policy. If DHHS is now suggesting that the IRB review process should not exceed certain ceiling criteria, CIRB recommends that this expectation be set forth clearly in the regulations.

A. Proposal to Move From Exempt to Excused

CIRB strongly objects to the proposed change of terminology from "exempt" to "excused." This will only further confuse the regulatory intent. The concept of exemption was introduced in the 1981 publication of 45 C.F.R. Part 46:

> The regulations contain broad exemptions for educational, behavioral, and social science research that involves little or no risk to research subjects. These exemptions constitute a major deregulation from rules in force at the present time. They exclude most social science research from the jurisdiction of the regulations. The regulations substantially modify the existing HHS policy...by reducing significantly the coverage of this policy.

See 46 Fed. Reg. 8366, 8367 (Jan. 26, 1981). Such studies remain exempt from IRB review, and CIRB believes that "exempt" is the correct word in terms of IRB function. Historically, while not dictated in the Common Rule, most if not all institutions impose on the investigator responsibilities to the subjects and the institution in connection with the conduct of "exempt" research.

The current "exempt research" regulation effectively allows institutions to have one person other than the investigator agree that the procedures fit an exemption category. Upon that determination, the IRB may be excluded from any review of risk, of benefit, of consent or of any other protection of subjects.

Some institutions, seeing little differentiation among the procedures assigned to the exempt and expedited categories, have elected to treat exemptions under an expedited review process. This equates to applying a single standard across multiple disciplines. Nothing from OHRP signaled that this was an inappropriate practice.

CIRB has some suggestions that may better advance use of the "exempt" category:

1. CIRB recommends that the specific exemption categories be removed from 45 C.F.R. § 46.101 and be placed into a list similar to the list created for expedited review pursuant to 45 C.F.R. § 46.110(a). A modified and modernized list of exempt categories should be promulgated.

2. In support of an exempt status, the revised 45 C.F.R. § 46.101 should indicate that research on the exempt categories list is presumed to present much less than minimal risk. No presumption of risk level is stated

currently. The unspoken/unstated historical presumption has been that procedures in the exempt category clearly pose less than minimal risk while the expedited review category required affirmation that the study and its procedures pose no more than minimal risk. Further, if minimal risk is now to be presumed for the expedited review category, as suggested in the ANPRM, CIRB recommends that this presumption be clearly stated.

3. Guidance should make clear that exempt studies are human subject research for which IRB review is not required by regulation.

4. OHRP should provide an alternative mechanism to assure that the investigator's categorization of the study as exempt is appropriate. If the regulations do not expect institutions to generally review all such decisions, the regulations should further clarify that the investigators, not the institutions, are responsible for such decisions.

In addition, CIRB has several questions about the new proposals concerning exempt research.

1. What is the proposed remedy if the investigator files the one page exemption claim (the registration), the study starts, and the claim is rejected upon later audit by the institution?

2. If there is liability as a result of something that happened during a study deemed "exempt" by the investigator which may not have qualified, what defense would there be against the claim that the institution either knew or should have known of the risk?

3. We note that many IRBs grant exemptions for Department of Education ("DOE") funded research. However, the DOE is not mentioned in this ANPRM. Will DHHS consult with agencies such as DOE as it considers modification to the exempt categories?

B. Expedited Review

In the ANPRM, DHHS/OHRP is asking for authority to update the expedited review categories. However, OHRP already has the authority to update the categories, and this activity was last undertaken in 1998. See 63 Fed. Reg. 60,364 (Nov. 9, 1998). CIRB offers the following additional comments on the proposals concerning expedited review.

1. If there is a presumption that everything in the expedited review categories is no more than minimal risk, what differentiates the exempt and expedited categories? What is the theory or standard for assigning one set of procedures to the exempt category and other procedures to expedited review if all are presumed to be no more than minimal risk?

2. Within expedited review categories, an experienced IRB member must affirm that the procedures pose no more than minimal risk. Each of us has encountered situations where the procedures fit the categories but there were

questions about risk. Thus, CIRB believes that minimal risk should be affirmed by the expedited reviewer and should not be presumed for the expedited review category.

3. In the alternative to 2 above, if minimal risk is presumed and if the review criteria are minimized, perhaps such studies should be incorporated under the exempt category. In this way, the solo non-IRB reviewer should simply evaluate whether the study meets the requirement for exemptions.

4. The inconsistency in application of the definition of minimal risk in different institutions is often a reflection of the institution's ability to work with the risks posed and, as such, is an appropriate issue in relation to local conditions.

5. That all studies should meet all review criteria has been the basis for determination letters and audit results for 50 years. It should be clear by now that each of the elements can and should be applied in a manner appropriate to the study. The ANPRM proposal to create two sets of criteria - one for studies that are to be reviewed only once, and one for studies to be reviewed initially and then at least annually - creates additional and unnecessary burdens for reviewers and leaves room for potential errors. See CIRB's additional discussion on this issue below in Section II.C.

CIRB welcomes reasonable and responsible streamlining of documentation requirements as they concern expedited review, and supports the development of guidance that encourages best practices with lessened documentation and process.

C. Eliminate Continuing Review for Expedited Studies

Both OHRP and FDA guidance have made clear very recently that the continuing review criteria for expedited studies should be the same as those reviewed by the convened IRB. See 76 Fed. Reg. at 44,517. The ANPRM now is suggesting doing away with continuing review for expedited studies altogether. CIRB rejects this proposal for the following reasons:

1. CIRB notes that social, behavioral, and educational research ("SBER") studies change more over a short time than clinical studies do over much longer periods. Thus, review to determine that the study continues to meet regulatory criteria is probably more necessary for SBER studies than other types of studies.

2. It is CIRB's experience that while drug research may yield more serious events, SBER studies yield a greater number of complaints. CIRB further notes that sponsored drug studies generally require a high level of investigator training about Good Clinical Practice ("GCP"), while it would appear that GCP training associated with SBER studies may be less rigorous. This potential lack of training in the SBER arena could account for the perceived variability in compliance, and more non-compliance and violations.

3. CIRB notes that IRBs are charged with more than risk reduction and that investigator practices with regard to subject welfare and informed consent are not evaluable until after the study is started; that is, at the time of continuing review.

4. The proposal suggests that a reviewer (presumably at the time of initial review) would need to make a specific determination and justification for requiring continuing review, and to specify how frequently such review would be required. Implied is that the reviewer has noted a concern which, in most systems, would require referral to the full board.

In the alternative, CIRB suggests the following:

1. OHRP guidance can be altered regarding expedited review as necessary. For instance, there is no reason to seek continuing review during data analysis.

2. CIRB recommends the issuance of a Joint OHRP/FDA guidance explaining that studies qualifying for expedited continuing review can employ a streamlined process requiring less documentation than that required for review by the convened IRB, and perhaps performed by the IRB administrator. For example, the review could be limited to determining that no change in the research plan has occurred.

D. Written Consent for Biospecimens

The matter of biospecimens and consent is complicated by the fact that it is expected that in a short time, privacy of a deidentified sample cannot be assured due to swiftly improving technologies. Thus, CIRB believes this matter invites a separate rulemaking to fully define the issues. Nonetheless, CIRB provides limited comments on this issue both here and in other sections of this letter addressing biospecimens.

Whether or not to require written consent for use of residual specimens taken for clinical purposes has been the subject of multiple discussions. Most agree that people wish to be advised of such use, but would also agree to such use if asked. This proposal goes further by requiring individual written consent rather than, for example, a universal notice or an informational notice with an option to opt-out. See 76 Fed. Reg. at 44,519-20. What is not discussed is any recognition of the burden of the requirement on both subjects and sites.

CIRB has the following questions about this proposal:

1. If there are no decisions made but only one choice given, is there really any choice at all? The choice could become the same as a Health Insurance Portability and Accountability Act ("HIPAA") Authorization in which one must sign to obtain service. If there is no choice, should this proposal be about notice?

2. If there are decisions to be made about eventual use or restricted uses as is found in the current templates, then the choices must be recognized. How are the choices tracked? How might some specimens be either blocked from leaving the acquiring institution or tracked with any restrictions? This could require significant data accompanying each specimen. CIRB recognizes that many sponsors who collect specimens, as well as companies that specialize in biospecimen storage and management, have developed some highly technical mechanisms for tracking permissions in consent. However, it may be difficult for smaller entities to adopt such tools.

3. How is the chain of evidence of the written consent document to be managed? Where is the original written document to be stored and how is access or information about it made available to the eventual end user?

4. As discussed above, unmentioned in the ANPRM is that with emerging technologies it will soon be the case that all specimens must be considered to be possibly identifiable. If specimens can be tracked and identities learned, there is no argument available that the end user does not know whose specimen contributed to a major breakthrough. Should or must such "donors" be included in a compensation package?

E. Informational Risks

The ANPRM suggests that if the only risks associated with a study are informational, then application of privacy requirements similar to those set forth in HIPAA should apply. See 76 Fed. Reg. at 44,524-25. However, if it is determined that the studies in the exempt and the expedited categories pose no more than minimal risk, even with inclusion of informational risk, then there should be no reason to impose the burdensome, and in some cases inappropriate, requirements of HIPAA.

In addition, while HIPAA identifiers could provide a starting point for SBER studies, they are insufficient when small cells, classrooms for example, are used. Further, limited data sets are useful but may conflict with requirements such as those set forth in the Protection of Pupil Rights Amendment. Moreover, HIPAA data security requirements require some levels of sophistication and computer power that may be inappropriate for studies and institutions working in the low risk arenas.

Finally, even while most information studies are low risk, most IRBs can identify studies that the investigator presumed had low informational risk but, in fact, the risk was greater than minimal. Thus, DHHS should carefully consider whether "informational risk" only is a sufficient criterion to determine that the study should be exempt.

III. STREAMLINING IRB REVIEW OF MULTI-SITE STUDIES

As DHHS knows, in the fall of 2004, the Secretary's Advisory Committee on Human Research Protections ("SACHRP") suggested a workshop on "Alternative Models of IRB Review." The conference was held on November 17-19, 2005 in Washington, DC and was followed by a "National Conference on Alternative IRB Models: Optimizing Human Subject Protection" on

November 19-21, 2006. The conferences highlighted a range of practical (and workable) review models, including independent (commercial) IRBs, which meet the needs of a variety of research programs.

Independent IRBs have provided quality human research protections oversight for over four decades and representatives of independent IRBs serve in leadership roles in regulatory, legislative, education, and public policy. The independent IRB community continues to provide a pivotal function in the conduct of quality multicenter research leading to timely approval of medications for the benefit of society. Because of the highly visible profile of independent IRBs, their involvement in the entire clinical trial enterprise has been transparent and open to scrutiny. Moreover, the independent IRB model continues to be identified as one to be emulated as an oversight process that enhances human research protections.

A. Mandating Central IRB Review

The ANPRM asks for commentary on the central review model and particularly whether there are advantages in mandating its use for domestic multi-site research studies. See ANPRM Question 30, 76 Fed. Reg. at 44,522. Mandating the use of a central review model eliminates the ambiguity associated with multiple oversight committees and allows regulatory and other interested groups to hold one entity responsible. Evidence to date indicates that simply "encouraging" an institution to participate in a central review model has been unsuccessful.

B. Central IRB Review versus Multiple IRB Reviews

The ANPRM states:

> Many commentators claim that multiple IRB reviews do not enhance the protection of human subjects and may, in fact, divert valuable resources from more detailed reviews of other studies. Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most clinical studies can be addressed through mechanisms other than local IRB review. For research where local perspectives might be distinctly important (e.g., in relation to certain kinds of vulnerable populations targeted for recruitment) local IRB review could be limited to such consideration(s), but again, local IRB review is not the only mechanism for addressing such issues. The evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent document and process generally do not require the unique perspective of a local IRB.

Id. This quote encompasses three distinct factors.

1. *Do multiple reviews enhance the protection of human subjects?*

It can be argued that each review adds more protections. This would be useful if such additional experience were captured and used successfully. As currently practiced, the

contributions of later IRBs are viewed as distractions and, as pointed out in Dr. Jerry Menikoff's article, "Streamlining Ethical Review,"[5] serve to teach those IRBs that their opinion is sought but not valued, which can ultimately lead to apathy.

2. *Do multiple IRB reviews divert valuable resources from more detailed reviews of other studies?*

CIRB believes that multiple reviews indeed divert resources from other studies. This is particularly true where later IRBs can only accept or reject a proposal.

3. *Should local perspectives be the primary reason for local IRB review or can those considerations be managed through other means?*

CIRB recommends that the institutions themselves should dictate how to implement internal review of their interests. If they so choose, they can elect to use an IRB, or some other abbreviated method to internally assess human subject protections. For select studies, such as investigator initiated/high risk studies (e.g., those that may result in stigmatization of local or targeted populations), the established processes (e.g., as defined by contractual relationships or an IRB authorization agreement) should strictly identify how such issues will be addressed.

AAHRPP recently addressed local perspective in a Tip Sheet entitled "Tip Sheet 24: Relying on An External IRB." See AAHRPP's Tip Sheet 24. In the Tip Sheet, AAHRPP recognized the importance of developing "a formal written agreement which clearly delineates the roles and responsibilities of each party," when organizations choose to rely on an external IRB. Id. With regard to local context issues, AAHRPP states that part of the role of the relying organization and researchers is to "provide the IRB with any local context issues relevant to the research protocol." Id. AAHRPP further acknowledged that IRBs can obtain local context information "through membership, consultants, or [other] required mechanisms." See AAHRPP's Advance: Relying on Another Organization's Institutional Review Board.[6] CIRB believes that these recommendations have already been adopted by most, if not all, AAHRPP-accredited IRBs.

C. Legal Liability

The ANPRM also asks to what extent concerns about regulatory and legal liability contribute to an institution's decisions to rely on local IRB review for multi-site research. See ANPRM Question 32, 76 Fed. Reg. at 44,522.

CIRB believes this is a false perception that continues to be propagated. Without doubt, an institution always remains responsible for its program of subject protection. However, there is no evidence that an institution incurs regulatory or legal liability because an institution elects to

[5] Millum, J. et al., Streamlining Ethical Review, *Annals of Internal Medicine* 153,10: 655-657 (2010).

[6] *Available at* http://advance.aahrpp.org/2011/09/relying-on-another-organizations.html.

rely on an independent/central IRB. See FDA Guidance for Industry, "Using a Centralized IRB Review Process in Multi-center Clinical Trials" (March 2006)[7] on the use of a central IRB for multi-center studies.

D. IRB Shopping

Finally, the ANPRM brings up the concern of "IRB shopping." See ANPRM Question 34, 76 Fed. Reg. at 44,522. As DHHS may recall, FDA reviewed this issue and concluded that IRB shopping does not occur at a level to warrant rulemaking. See 71 Fed. Reg. 2493 (Jan. 17, 2006).

Nonetheless, CIRB members are careful to assure minimization of this possibility by requiring investigators and sponsors to reveal whether a protocol has been presented to or withdrawn from another IRB and if withdrawn, why.

IV. IMPROVING INFORMED CONSENT

As an initial matter, CIRB believes that the multiple root causes of the ever growing consent documents are quite different from the root causes of the process and risk-oriented issues raised throughout the ANPRM. The ANPRM suggestions focused first on length and grade level considerations. Although the IRB may strive for simple and straightforward consent documents, it is currently an uphill fight. There are myriad factors to consider including the role of attorneys, the National Cancer Institute Central IRB risk sections, and 16th grade language accepted in recent FDA/OHRP draft guidance on exculpatory language. Further, CIRB notes that improved consent documents must be accompanied by improved methods of considering the consent process and the means by which people make decisions to participate. Thus, CIRB strongly suggests that this issue be addressed in a separate proposal. Nonetheless, it provides its general comments on this important issue below.

A. Improving Consent Forms

CIRB presents the following comments on the proposed modifications being considered in the ANPRM to improve consent forms. See 76 Fed. Reg. at 44,523.

1. *Proposal: Prescribing appropriate content that must be included in consent forms with greater specificity than is provided in the current regulation.*

   CIRB believes that more specificity would help IRBs with review by enhancing knowledge of particular topics of concern. However, it is important to identify who would determine the specifics and how they would be determined to assure that this specificity does not result in increased length. Informed consent forms should contain adequate explanations regarding data security, or lack thereof.

[7] *Available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm.

2. *Proposal: Restricting content that would be inappropriate to include in consent forms.*

Restricting inappropriate content will help reduce length of the informed consent form, will eliminate confusion for subjects, and will help research staff involved in the informed consent process. For example, consent forms can be modified to make optional the "alternatives" section so that it is used only when there are alternatives. In addition, modifying the contact information section to remove the explanation of when to call the investigator and when to call the IRB may mitigate confusion and unnecessary language. Instead, merely informing the subject to call the investigator first, the clinical coordinator second, and then the IRB if the issue is not resolved might be helpful.

3. *Proposal: Limiting the acceptable length of various sections of a consent form.*

While admirable, this task may be difficult for some studies. Guidance is needed to address different methods to reduce length of the main form and to provide specifics for inclusion of sections such as addenda, tables with visit expectations, etc. Shorter length of informed consent forms should increase ease of understanding for the subjects. For example, not all risks need to be listed; many can be generalized, and risks can be limited to those due to participation.

4. *Proposal: Prescribing how information should be presented in consent forms, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form.*

CIRB supports this type of initiative. Better organization of the informed consent form would provide information more clearly to subjects. Further, appendices and/or addenda may be useful in increasing readability. However, DHHS must keep in mind that different fields and disciplines may require different structures.

5. *Proposal: Reducing institutional "boilerplate" in consent forms.*

This could be addressed by institutions with inclusion of institutionally required language in an addendum, which would result in less confusion in the informed consent form.

6. *Proposal: Making available standardized informed consent form templates.*

Standard templates would require clearly defined content and format. However, the question of broader interest is who would be responsible for the design of the template? Federal agencies? IRBs? Central IRBs? This undertaking would be time-consuming and difficult.

There are pros and cons to a standardized informed consent concept. For example:

a. Informed consent forms would be easier to produce when starting with a well-designed template. A recognizable format would be easier for IRBs, researchers, and research staff, to understand content, from study to study, for both review and consenting purposes.

b. A standardized format may not allow a means to adequately address unique study features. A standardized format may contribute to "blind" reliance on the template rather than assuring that all the required information is adequately addressed.

c. Standardized templates often have all possible issues with the instruction to delete those not used. Deletion is more difficult than inclusion. An example is the growth of templates used for genetic specimens that are now four pages.

If DHHS decides to undertake the development of standardized templates, however, CIRB suggests the following. Only those items specifically required by the applicable regulations and guidance documents should be included. Detailed discussions, such as those regarding indications, visit schedule, lab specimens, standard of care alternatives and adjunct treatments, and HIPAA, should not be included. Standard of care details can be placed in a separate "take home" information sheet, and schedule and procedure details can be provided in another information sheet. Discussion of the indication/disease should be conducted by the medical staff. Institutionally required contractual language can be included in a separate contract document.

Further, informed consent templates should be identified as exemplars for voluntary adoption by the IRB, as opposed to a regulatory requirement. CIRB recommends that if the template development process is undertaken, it should involve the expertise of the IRB community, and CIRB would be pleased to assist on an informed consent template development working group.

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

It is stated that the current regulations have proven to be confusing for some IRBs and many investigators. The general requirements for informed consent are found in 45 C.F.R. § 46.116. 45 C.F.R. § 46.116(a) and (b) outline the basic and additional elements of informed consent. 45 C.F.R. § 46.116(c) and (d) provide the flexibility, under specific circumstances, for the IRB to waive some or all of those elements, or alter some or all of them, or waive obtaining consent altogether. However, the requirements for waiving informed consent are often confused and could be revised to be clearer. Alternatively, they could be addressed in guidance.

45 C.F.R. § 46.117(b) and (c), *Documentation of informed consent*, also is confusing for some. 45 C.F.R. § 46.117(b) discusses the format of the consent form. It can be a written full consent

form, but read to the subject, with signatures obtained, or a short form documenting that the information was provided orally, with signatures obtained. In 45 C.F.R. § 46.117(c), a provision is made to waive the documentation (signature). 45 C.F.R. §§ 46.116 and 46.117, addressing waiver of informed consent and documentation of informed consent, could be revised more clearly so that all the possible flexibilities are understandable and instructive.

Further, neither the ANPRM or current regulations address present (and future) technological advances, which have provided scenarios where informed consent may not be feasible, or techniques for documentation that may not meet the "signature" requirement, such as web-based surveys. IRBs and researchers currently struggle with regulatory acceptability of signatures that are not pen and ink. The revised Common Rule must be updated to reflect, and anticipate, technological advances.

Finally, modernization of the policies surrounding informed consent documentation requirements should be undertaken with regard to vulnerable populations as set forth in Subparts B and D of the Common Rule. For example, DHHS may consider providing guidance regarding the application of the general requirement under Subpart D that both parents consent for a minor to the current society in which a significant single parent population exists.

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

This section of the ANPRM addresses the currently confusing consent options regarding biospecimens and future use. See 76 Fed. Reg. at 44,523. HIPAA and the Common Rule are in conflict regarding future use, in some cases depending on identifiability of the specimens. HIPAA requires separate study-specific authorizations for future use, while the Common Rule may allow unspecified future use. Harmonization of the rules would be useful to researchers planning studies and IRBs reviewing protocol applications.

Much of the research with biospecimens is global in nature, and currently, there is no consensus about the regulations that govern biospecimens and future use. Consent models and ethical recommendations range from strict (specific informed consent) to basically unrestricted use (broad consent).[8] The complex nature of issues really defies a simple approach. There is a need for international standardization, particularly in light of what the Council of Europe described as the "increasing cross border flow of biological materials of human origin and data."[9] CIRB strongly recommends that the scope, complexity, and international significance of this topic warrant its own, separate inquiry.

In the meantime, guidance regarding what is appropriate informed consent for the storage of biological samples for specific research studies and future investigations would be a significant contribution. As noted in CIRB's comments in Section II above, biospecimen collection and research has become a common element of the vast majority of clinical research protocols.

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[8] Maschke KJ, Navigating an ethical patchwork—human gene banks. *Nat Biotechnol* 5: 539–545 (2005).

[9] COE, *Recommendation of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin*. Strasbourg, France: Council of Europe (2006).

The ethical and regulatory issues raised by biospecimen research that need to be addressed in any consent process include the ownership of biospecimens obtained from medical interventions or research projects; the potential use of the biospecimens and related data; defining the risks to individuals or racial or ethnic groups; the confidentiality of original and subsequent data; third party access; commercial developments, such as diagnostic procedures and drugs; and intellectual property rights, such as patents and licenses.

Further, review of the acceptability of proposals for future unspecified use of biospecimens seems to place the IRB in a position where it must consider, for the purpose of evaluating, whether there is an adequate consent process, and the possible long-term effects of applying knowledge gained in the research – something that the Common Rule currently states does not fall within the purview of an IRB's responsibility. For instance, whether the future use could support development of a product or procedure that the subject would violently object to if he or she had known. There is a need to clarify the boundary for this type of issue in particular.

The following are categories that might be presented in a standard consent with yes/no options (these may not be feasible, however, in many acquisition situations):[10]

1. The samples collected during <describe> may be retained by <institution/bank/organization>.

2. The samples may be used for the specific purposes of this study.

3. The samples may be used now or in the future for all kinds of research that, directly or indirectly, relates to the purposes of this study.

4. The samples may be used now or in the future for all kinds of research, including research not related to the purposes of this study.

5. The samples, data and any research study results may be used for the development of commercial products, without any financial benefit to me.

Many advocate finding a balance by using more than one standard approach – a broad or restricted/specific informed consent as appropriate.[11] In some cases, particularly those involving the collection, retention, and use of samples required by state law for public health programs (e.g., newborn screening bloodspots), a simple notification may be a viable approach.

V. STRENGTHENING DATA PROTECTION TO MINIMIZE INFORMATION RISKS

As noted in the ANPRM, privacy protection is a powerful promoter of participation in research. See 76 Fed. Reg. at 44,524. Security breaches are problematic inherently because they

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[10] Knoppers BM, Consent revisited: points to consider. *Health Law Rev* 13: 33–38 (2005).

[11] Hansson MG, et al., Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* 7: 266–269 (2006).

undermine public trust, which is essential for patients to be willing to participate in research. The proposal to strengthen data protection would do so through revised data security and information protection standards, and by applying the HIPAA Privacy Rule standards to all research.

Specifically, the proposal suggests that human subjects regulations 1) adopt the HIPAA Privacy Rule standards defining de-identified information, limited data sets and data use agreements, as determinants of whether the information collected is "identifiable" such that the humans become human subjects, and 2) adopt standards modeled on the HIPAA Security Rule whenever data are collected, generated, stored, or used. See 76 Fed. Reg. at 44,525.

A. Common Definitions

CIRB believes that common definitions between the HIPAA Privacy Rule and human subject regulations would be helpful. However, level of identifiability cannot be the only standard used to calibrate the level of security protection required. Privacy technology experts assert that any remaining attributes after removal of "personally identifiable information" can be used to identify someone, as long as they differ from individual to individual.[12] Therefore, level of identifiability is a necessary standard, but insufficient by itself.

It is also necessary to distinguish between different types of databases and where they reside. The quantity and attractiveness/sensitivity of data remaining after de-identification,[13][14] and whether or not the database exists within an open or closed system, must also be considered. It is much easier to match data to outside information when there are more records indicating preferences, behaviors, and/or physical and medical attributes. Large databases are considered more identifiable than small, regardless of "de-identification."

Databases created and maintained in an "open system" for the purpose of access by third parties require higher security provisions than databases created and maintained within a "closed system" for the purpose of use and analysis within the bounds of an organization with no intent to share outside of the organization.

Therefore, security protections should not be calibrated based only on level of identifiability, but also on whether the researchers are the owners of large databases or are users that have access to large databases, the attractiveness/sensitivity of the data, and whether or not the data exists within an open or closed system.

Of note, DHHS' decision to consider whether all research involving primary collection and storage of biospecimens and secondary analysis of existing biospecimens should be categorized

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[12] Narayanan, A., et al. Privacy and Security: Myths and Fallacies of "Personally Identifiable Information." *Communications of the ACM* 53:6 (2010).

[13] Ohm, P. Broken promises of privacy: Responding to the surprising failure of anonymization. 57 *UCLA Law Review* 1701 (2010).

[14] Sweeney, L. Weaving technology and policy together to maintain confidentiality. *J. of Law, Medicine, and Ethics* 25: 98-110 (1997).

as identifiable information is consistent with this train of thought. These types of databases contain very large amounts of information, regardless of the state of regulatory de-identification.

B. Re-Identification

Recognizing the current power of re-identification technology, it does not seem necessary to create a mechanism to iteratively reevaluate over time what makes data de-identified. As stated previously, we suggest that it is more helpful to acknowledge that we are already at the point where successful "de-identification" of data cannot be guaranteed. If we do not overvalue de-identification as a protection nor solely depend upon de-identification as the standard to calibrate security protection, it is simply not necessary.

C. Applicability of HIPAA Security Rule

HIPAA Security Rule standards are not appropriate for all types of research studies or investigators. See ANPRM Question 54, 76 Fed. Reg. at 44,525. Subjects would not be sufficiently protected by the blanket administration of these standards. Moreover, the standards are too high for some types of research data and not realistic for some researchers who rely on personally identifiable information.

The problem is that the HIPAA Security Rule does not define a specific, concrete, strict standard. It requires a risk assessment followed by implementation of "reasonable and appropriate" measures to secure the systems holding the data. It does not define the adequate measures for various types of data and risk, nor provide instruction on how to implement them. Security implementation requires specific expertise, and most researchers that rely on collection of personally identifiable information do not have this expertise in-house, and it may be prohibitively burdensome from a financial perspective to require that they do so.

D. Alternative to HIPAA Security Rule

As an alternative, we suggest that the regulations mandate a minimum floor of specific, concrete, safe data handling practices for every data handler. However, the floor cannot be too high. Even the best computer security solutions are bug prone and people prone, and are expensive to create and deploy.

1. The minimum floor should include encryption for data stored in removable media (e.g., jump drives, laptop computers) or transmitted in electronic form, access control for records stored in paper or electronic form (e.g., passwords and locked paper storage), and a self-monitoring/auditing program as outlined below.

   In general, databases created and maintained within a closed system, that are accessed, used and analyzed totally within the bounds of an organization, with no intent to share outside of the organization, would require implementation of only these specific, concrete, minimum floor security protections. Boot-strapped to these minimum-floor standards, we agree that IRB review of information protection measures would not be required for low-risk studies

posing only informational risks, with the provision that subjects are provided information regarding how the information will be collected and used.

2. Strong protection, including audit trails, breach notification requirements, and prohibition from attempting to re-identify subjects (for data in limited data sets) should be required for databases containing identifiable information or databases that intend to share data with other researchers. We agree that the "above the floor" standards could be modeled after HIPAA procedural and security standards. However, we suggest that the responsibility for implementation be placed with the research sponsor/owner of the database (or institution if the research is federally funded). These are the entities that control the data handling, and we suggest that they be required to evaluate the contributing investigators' security measures for collection and transmission of data prior to engagement of any investigator (data contributor). This would limit the burden falling on the investigators, a great many of whom operate in small offices without access to sophisticated security expertise. The security expertise of the database sponsor/owner would be relied on for the evaluation of the adequacy of security measures relative to investigators' data handling.

IRBs should prospectively evaluate the data protection and security protections in full board studies and have access to the requisite data security expertise. IRBs should also confirm that the sponsor has evaluated each contributing investigator's data security structure relative to the research project. Indeed, there may be some variability in how IRBs evaluate data security measures. However, we suggest that this variability is much less than if each investigator was independently responsible for determining his/her own "reasonable and appropriate" security measures. If an investigator is creating a recruitment database separate from the study, the IRB would have to evaluate whether the investigator meets the minimum floor standards.

Information protection and security should remain a criterion for IRB approval of research.

3. We suggest that a requirement for self-monitoring and auditing compliance by investigators and/or institutions with data security measures would provide greater protection than retrospective audits by any other party. In essence, retrospective audits do not protect – they merely detect non-compliance after the potential harm has happened.

Periodic security audits conducted by members of the research team or institution are a routine feature of robust security administration within larger organizations. The audit is routinely performed by non-security, departmental personnel that take turns conducting the audits during off-hours. The audit uses criteria developed by security administrators. Executing these audits does not take technical expertise. Any security deviations are documented

and reported back to security administrators, who, in turn, oversee a documented corrective action plan.

This documentation is then available and could be inspected as part of routine audits already conducted by regulators and others.

4. Finally, we suggest that the new plans be applied only prospectively to data secured in the future; they will do nothing to protect data that has been stored or disclosed in the past. A database, once released, can become easier to re-identify but never more difficult.

VI. DATA COLLECTION TO ENHANCE SYSTEM OVERSIGHT

A. General Comments

In an effort to reduce burdens on the investigator and to generate a central point of safety data collection to foster better analyses, DHHS is suggesting the expansion of a federal-wide portal to which investigators can submit safety data which will then be automatically delivered to "appropriate agencies and oversight bodies." 76 Fed. Reg. at 44,527. While CIRB applauds the goal of simplifying the current reporting requirements, CIRB has many questions about the proposed database, and central among those questions is whether the database would have the unintended effect of impeding important initiatives already implemented to streamline the process.

Over the past 10 years, both FDA and OHRP developed policies and guidance intended to assure that safety and other research-related problem reports submitted to the agencies and IRBs are both appropriate and meaningful. The agencies have further worked towards reducing the burden on IRBs by describing the limited subset of adverse event reports that should be submitted to IRBs as unanticipated problems involving risks to subjects or others ("UPIRSO"), and clarifying the definition of UPIRSO as it applies to non-adverse events. CIRB applauds these efforts and believes it would be a significant disservice to the research community and to subjects if these efforts are lost with the implementation of a central reporting location.

In its 2009 guidance for clinical investigators, sponsors, and IRBs on adverse event reporting requirements, the FDA noted: "The receipt of a large volume of individual AE reports without analysis of their significance to a clinical trial rarely supports an IRB's efforts to ensure human subject protection." See FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection (January 2009).[15] This guidance provided clear thresholds for determining when an event is reportable to the IRB and clarified the responsibility of sponsors to provide IRBs with meaningful safety data that informs the IRBs' decision-making and oversight of a clinical trial. Id.

The FDA guidance paralleled guidance on the same issue published by OHRP in 2007. See OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to

[15] *Available at* www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

Subjects or Others and Adverse Events (January 2007).[16] The OHRP guidance also provided much needed clarification regarding UPIRSO reports that are not adverse events but, of course, must be reported to the IRB. As a result of these guidance clarifications, IRBs report receiving fewer individual safety reports from investigators and sponsors, and this has significantly reduced the burden on IRBs to review meaningless adverse event data.

If the data collection proposal is not approached with care, CIRB is concerned that the recent advances could be hindered, and that proposed changes could have the unintended consequence of shifting the review burden for individual safety reports from the sponsor to the IRB. As discussed in the FDA's 2009 guidance, the sponsor is in the best position to properly analyze individual safety reports, whereas the IRB has insufficient information to properly conduct such reviews.

As a result, in order for CIRB and others in the community to be able to provide relevant comment on this proposal, DHHS must first provide additional details. CIRB has the following questions about the proposed change:

1. *Central Reporting Web-Portal*: Which agencies will be linked to the central database? How will reports to an agency not using the web portal be handled? Will the web-portal replace paper-based submissions, and will this impose Part 11 requirements on submitters as well as those receiving the reports?

2. *Reporting Requirements*: Will investigators be required to report to the central database and also to the FDA, the sponsor, and the IRB? Will the proposed system replace FDA's existing databases and reporting requirements? Will the proposed system replace the requirements for investigators to report to the IRB unanticipated problems posing risk to subjects or others? What information must be reported to the web portal, and how will it be submitted?

3. *Analysis of safety information*: Who will conduct the integrated analysis and comparative studies of adverse events reported through the web-based portal? Will the system be designed to filter only information that meets threshold requirements for reporting? How will important safety data and information be communicated to the IRB?

B. Response to Selected Questions Raised in the ANPRM

DHHS asks whether the scope of events that must be reported under current policies, including the reporting of certain "unanticipated problems" as required under the Common Rule, is generally adequate. See ANPRM Question 67, 76 Fed. Reg. at 44,528.

As discussed in our initial comments, requiring investigators to report all adverse events through the web-based portal could have the unintended consequence of increasing the burden to the investigator and to IRBs. The scope of reporting to the IRB should be limited to UPIRSOs. Moreover, as discussed above any change in this area must keep in mind that not all UPIRSOs

[16] *Available at* http://www.hhs.gov/ohrp/policy/advevntguid.html.

qualify as adverse events, and thus, DHHS must consider whether the central database will accommodate these non-adverse event reports as well.

DHHS also acknowledges that there are a variety of possible ways to support an empiric approach to optimizing human subject protections, and asks whether it is desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies. Id.

Again, the unintended consequence of this reporting requirement may be an undermining of the recent advances by FDA and OHRP in clarifying the reporting requirements.

C. Support for Certain Proposed Changes to Enhance Data Collection and Oversight

While CIRB has many questions about the proposed central reporting database, it supports the underlying goal to enhance data collection and oversight, including the following proposed changes set forth in the ANPRM:

1. Use of 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; and

2. Harmonizing safety reporting guidance across all federal agencies, including harmonizing terminology and clarifying the scope and timing of such reports.

VII. EXTENSION OF FEDERAL REGULATIONS

A. Extension of Common Rule to All Research is Unnecessary

DHHS asks whether the Common Rule should be extended to all research that is not federally funded at a domestic institution that also receives some federal funding for research with human subjects from a Common Rule agency. See 76 Fed. Reg. at 44,528.

CIRB supports the important goal of harmonizing regulations and guidance by creating uniform, but flexible standards that apply to all human subject research. However, CIRB does not agree that the Common Rule should automatically extend to all non-federally funded research conducted at an institution that receives some federal funding for research with human subjects. The statement made in the ANPRM fails to explore the implications of an extension of the Common Rule of this type. The proposed solution is unnecessary and will not accomplish the goal of ensuring human subjects are adequately protected.

Mandatory application may not adequately take into consideration the type of research being conducted and the nature of risk involved in the study. As it is currently written, and even with the proposed changes in place, the Common Rule will not be appropriate for certain types of research. An institution's ability to conduct certain research (such as innovative social or behavioral research) may be severely restricted, and specific regulatory requirements may be inappropriate or unnecessary. Further, if the regulations are broadened to cover all types of

research, this may result in inappropriately broad standards that fail to provide meaningful standards an institution or researcher may use to determine if their actions are compliant.

The proposed application of the Common Rule to all research also may be unnecessary because many institutions already have policies in place that are:

- Substantially equivalent to the federal regulations;
- Based on ethical standards that take into consideration the nature and level of risk of a study being conducted at the institution; and/or
- In compliance with applicable accreditation standards that apply to research.

CIRB also is concerned that an extension of the Common Rule may create an undue burden on institutions (and the government) without adding additional protections for human subjects. Because such studies would become subject to a Common Rule agency's scrutiny, in order to remain compliant, an institution may need to take additional steps, including hiring additional compliance officers or IRB administration staff or adding additional IRB meetings. Steps like these will increase the financial burden, which may ultimately stifle research.

Finally, CIRB questions the authority of the agency to extend the Common Rule to all research conducted in an institution that receives some federal funding for human subjects research. As the DHHS undoubtedly knows, a federal agency must have statutory authority to regulate an activity. While CIRB recognizes that this authority exists as to federally funded research, research in support of an FDA marketing application, and certain other categories of research, if a clinical study does not fall within these limited situations there is a question as to the Common Rule agency's authority to regulate the non-federally-funded activity merely because some research at the institution is federally funded.

If DHHS seeks to extend the Common Rule as discussed above, significant changes to the rule will be required in order to address these concerns.

B. Research Subject Protections for All Research

Although CIRB does not support an automatic extension of the Common Rule to any institution that receives some federal funding for human subjects research, CIRB does agree that some level of oversight of all human subject research may be required. A proposed alternative to automatically extending the Common Rule to all human subject research is to require every institution that receives a certain amount of federal funding to go through some sort of process in order to ensure that subjects involved in non-federally funded research are protected. Some possible options include required training or a process in which the institution certifies that it has policies and procedures in place for conducting non-federally funded research. This process, however, must take into consideration the type of research being conducted and the nature of risk involved in the study. In addition, such a process should not unreasonably increase the financial burden on institutions and discourage important research. Nonetheless, DHHS must recognize that it must identify the necessary authorizing authority to implement even these minimal requirements.

VIII. CLARIFYING AND HARMONIZING REGULATORY REQUIREMENTS AND AGENCY GUIDANCE

DHHS requests comment on harmonization and clarification of human subject protection regulations across agencies. Id. As stated at the outset, CIRB believes harmonization is a critical initiative. With that said, CIRB understands that in some cases agencies may need unique guidance documents due to their different statutory missions, and the types of research supported by each agency. However, in many cases, these guidance documents are difficult to find, hard to understand, and may be duplicative. CIRB provides the following comments:

1. CIRB supports one set of guidance for all Common Rule agencies provided that the guidance clearly outlines any differences. This single set of guidance documents may include various guidance documents from each agency, but it should be readily available on all agency websites and should outline when each agency's guidance may apply.

2. CIRB urges DHHS and non-DHHS agencies to make information governing research requirements more accessible. Currently, guidance and other requirements for non-DHHS research are not always easy to locate on agency websites. Additionally, a number of agencies have more than a single document and it can be difficult to understand when each individual guidance document is applicable. Id.

3. DHHS points out the inconsistency in the privacy regulation in light of differing HIPAA and Common Rule requirements. CIRB recommends reevaluating whether a new approach for protecting privacy in health research would be more appropriate. If a new approach is adopted, CIRB supports changes to the current Privacy Rule in order to provide for more protections to subjects without impeding research.

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The ANPRM represents an important step towards addressing the need to modernize the government's approach to regulating clinical research and enhancing human subject protections. CIRB applauds this effort and yet cautions DHHS to approach this activity carefully to assure that tried and true tools to protect subjects are not inadvertently eroded in the process.

Respectfully submitted,

Cami Gearheart

Cami Gearheart
Chair

Enclosure (1)

APPENDIX TO COMMENTS SUBMITTED BY THE CONSORTIUM OF INDEPENDENT REVIEW BOARDS

DHHS Question	CIRB's Comments
Question 2 – Would the proposals regarding continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?	Pages 7-8
Question 20 – The term "Excused" may not be the ideal term to describe studies that will come within the proposed revision of the current category of exempt studies, given that these studies will be subject to some protections that are actually greater than those that currently exist. Might a term such as "Registered" better emphasize that these studies will in fact be subject to a variety of requirements designed to protect participants? We welcome other suggestions for alternative labels that might be more appropriate.	Pages 5-6
Question 23 – Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) above? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?	Pages 14-15
Question 24 (relevant part) – Are there specific types of these studies for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of "research" used in the Common Rule to exclude some of these studies, or a combination of both? And if the definition of research were to be changed, how should the activities to be excluded be defined (*e.g.*, "quality improvement" or "program evaluation")?	Page 2
Question 30 – What are the advantages and disadvantages of mandating, as opposing to simply encouraging, one IRB of record for domestic multi-site research studies?	Pages 9-10

DHHS Question	CIRB's Comments
Question 32 – To what extent are concerns about regulatory and legal liability contributing to institutions' decisions to rely on local IRB review for multi-site research? Would the changes we are considering adequately address these concerns?	Page 11
Question 34 – If there were only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of "IRB shopping" – intentionally selecting an IRB that is likely to approve the study without proper scrutiny – be prevented?	Page 12
Question 35 –What factors contribute to the excessive length and complexity of informed consent forms, and how might they be addressed?	Page 12
Question 37 – Would the contemplated modifications improve the quality of consent forms? If not, what changes would do so?	Page 12-14
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?	Pages 15-16
Question 49 – Is it desirable to implement the use of a standardized general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as public education campaign combined with a notification and opt-out process?	Page 15
Question 50 – What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens? How should the consent categories that might be contained in the standardized consent form be defined (*e.g.*, an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?	Pages 16
Question 55 – What mechanism should be used to regularly evaluate and to recommend updates to what is considered de-identifiable information? Beyond the mere passage of time, should certain types of triggering events such as evolutions in technology or the development of new security risks also be used to demonstrate that it is appropriate to reevaluate what constitutes de-identified information?	Page 18

DHHS Question	CIRB's Comments
Question 58 – Should the new data security and information protection standards apply not just prospectively to data and biospecimens that are collected after the implementation of new rules, but instead to all data and biospecimens? Would the administrative burden of applying the rule to all data and biospecimens be substantially greater than applying it only prospectively to newly collected information and biospecimens? How should the new standards be enforced?	19
Question 61 – Are there additional data security and information protection standards that should be considered? Should such mandatory standards be modeled on those used by the Federal government . . . .?	Pages 18-19
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?	Page 20 and 21
Question 69 – There are a variety of possible ways to support an empiric approach to optimizing human subjects protections. Toward that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?	Pages 19-21
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?	Page 22-23
Question 72 – To what extent do the differences in guidance on research protections from different agencies either strengthen or weaken protections for human subjects?	Page 24